CZECH HEAD AND NECK CANCER
COOPERATIVE GROUP

Pokroky v diagnostice a léčbě nádorů hlavy a krku

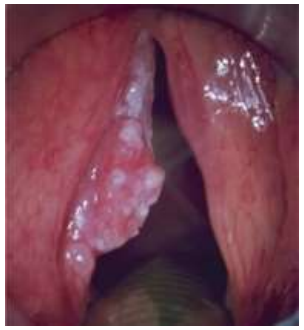
za posledních 5 let

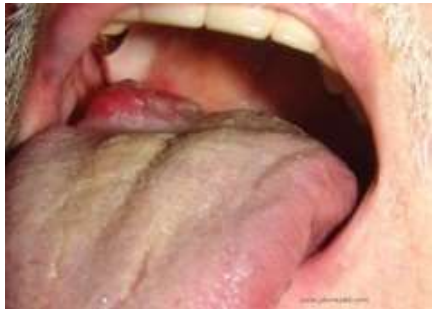
Doc. MUDr. Milan Vošmik, Ph.D.
Klinika onkologie a radioterapie
LF UK a FN Hradec Králové

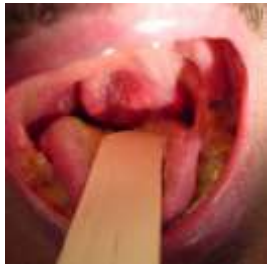
Co je nového v diagnostice a léčbě nádorů hlavy a krku?

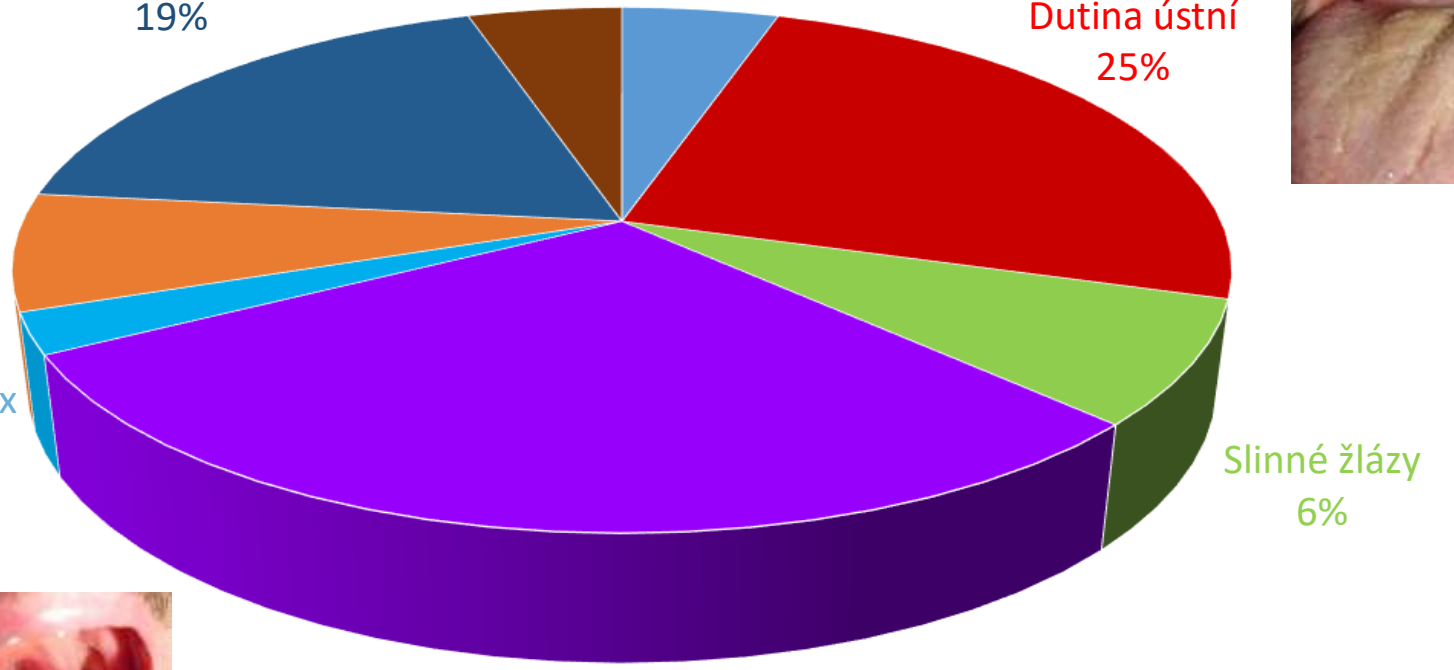
- Problematika HPV+ skvamózních karcinomů orofaryngu
- Rekurentní a metastatické skvamózní karcinomy H&N
- Karcinomy nosohltanu
- Karcinomy slinných žláz

Relativní incidence zhoubných nádorů jednotlivých ORL lokalit 2020



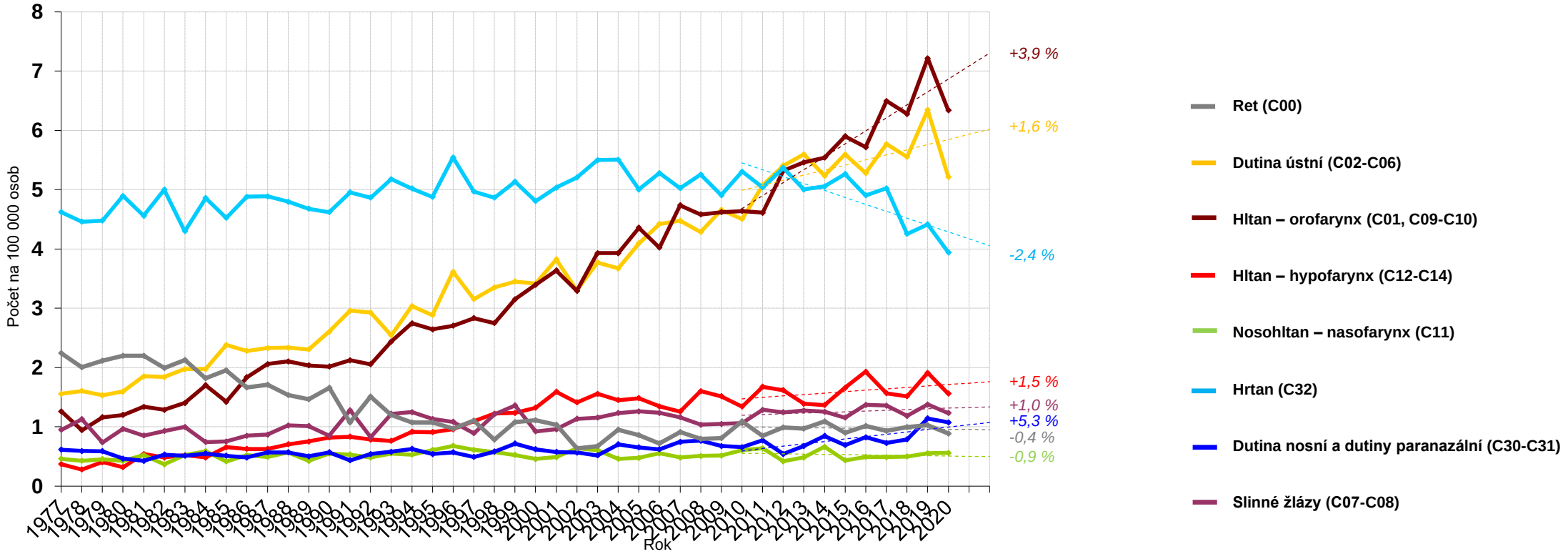






Trend incidence nádorů hlavy (C01–C14, C30–C32) a krku v České republice

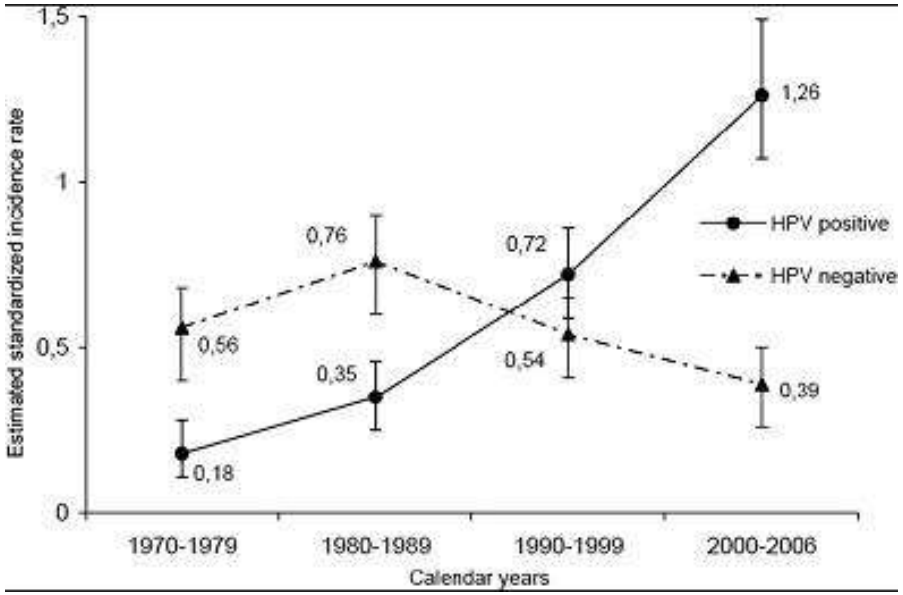
%: průměrná meziroční změna trendu za období 2010–2020



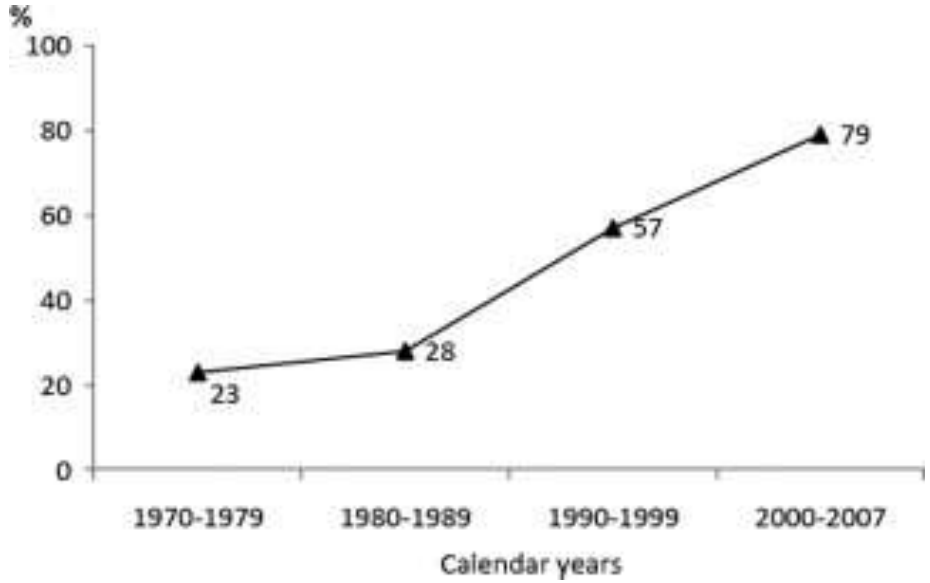
Zdroj: Národní onkologický registr, ÚZIS ČR, prezentováno se svolením RNDr. Jana Mužíka, Ph.D.

Data ze švédského registru:

podíl HPV pozitivních karcinomů tonsily z 23% (1970) na 79 % (2002-2007)



Hammarstedt et al. Int J Cancer 2006



Nasman et al. Int J Cancer 2009

Obdobná data z USA (Shiboski Cancer 2005) a Finska (Syrjanen *J Clin Pathol* 2004)

Počet HPV+ karcinomů tonsil **v ČR odpovídá asi 75%** (FNHK, nepublikovaná data)

Rozdíly mezi HPV pos. a HPV neg. SCHNC

	HPV +	HPV -
Lokalita	Orofarynx (tonsila, kořen jazyka)	Všechny lokality
Věk	Mladší	Starší
Rizikové chování	Větší počet sexuálních partnerů	Kouření, alkohol
Biologický stav	Velmi dobrý	Variabilní
T-stadium	Obvykle nižší	Variabilní
N-stádium	Obvykle vyšší	Variabilní
Histologie	Obvykle basaloidní typ	Různá
Zobrazovací metody	Často cystické změny v LU	Variabilní
Léčebná odpověď	Velmi dobrá	Variabilní
Prognóza	Příznivá	Variabilní
Molekulární vlastnosti	p16+, p53 WT	p16-, p53 mut
Incidence	Vzrůstající	Stabilní či klesající

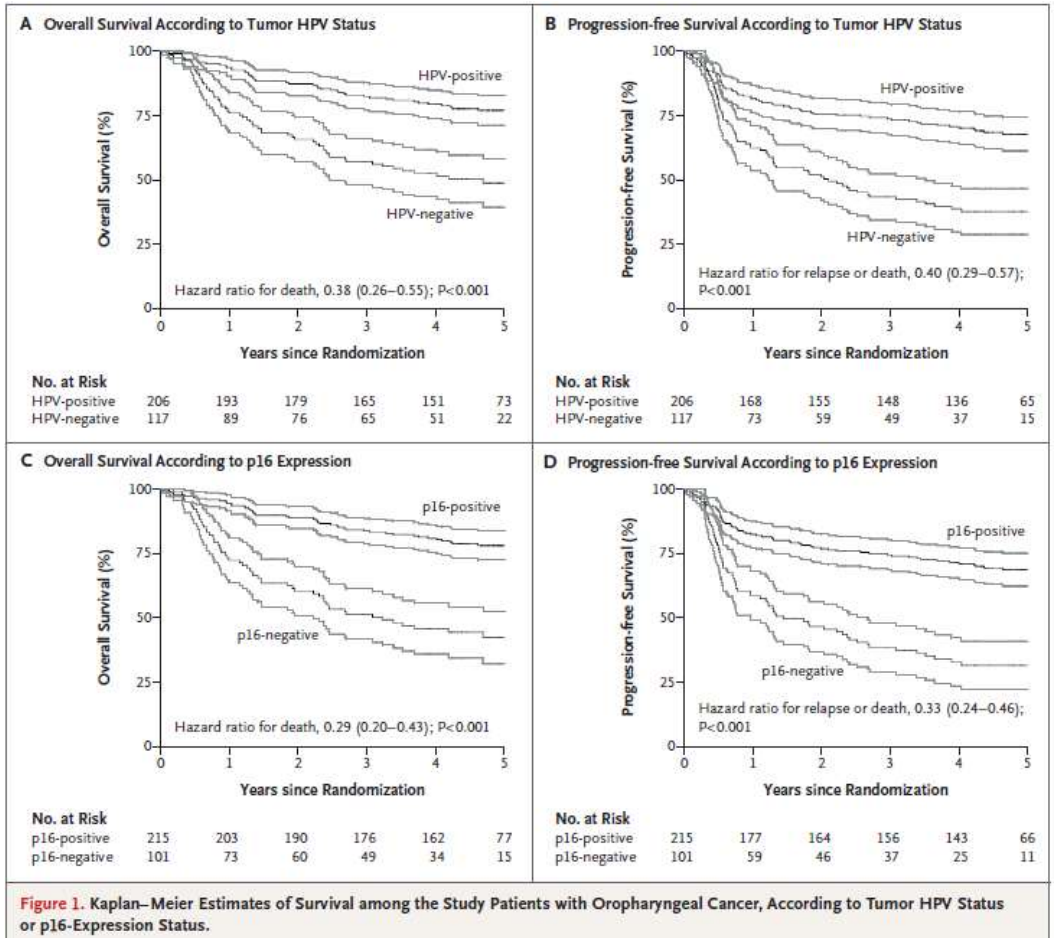


Figure 1. Kaplan–Meier Estimates of Survival among the Study Patients with Oropharyngeal Cancer, According to Tumor HPV Status or p16-Expression Status.

Post-hoc analýza studie RTOG 0129

Adaptováno podle Lim et al., Cancerforum 2015

Ang et al 2010 NEJM

HPV/p16 pozitivní karcinomy orofaryngu
Samostatná TNM klasifikace

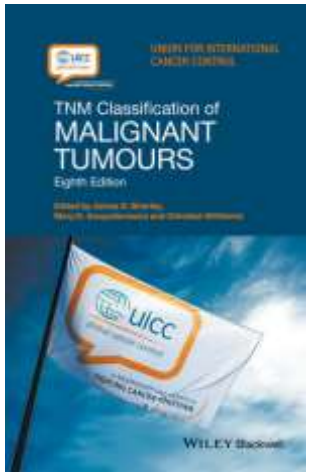


Table 1: Critical Changes in AJCC8 for Head and Neck Cancer Staging

Tumor Type	T Designation	N Designation
Oropharyngeal SCC		
HPV-related oropharyngeal SCC	New staging system for T, N, and prognostic groupings and used when oropharyngeal primary tumor is p16 or HPV positive	New clinical nodal table as follows: cN1: ipsilateral nodes cN2: bilateral or contralateral nodes; and cN3: nodes > 6 cm
	T4 no longer divided into T4a and T4b	New pathologic nodal table if neck dissection performed
Non-HPV oropharyngeal SCC	No changes	Addition of clinical ENE which determines N3b status
		New pathologic nodal table which also incorporates pathologic ENE
Nasopharyngeal carcinoma	Pterygoid muscle involvement now T2, previously included as part of *masticator space* and designated as T4	Level IV and Vb nodes now designated N3 disease with removal of term *supraclavicular fossa*
	Invasion to prevertebral muscles clarified as T2	Nodal masses > 6 cm also N3, removed N3a/N3b
	Invasion to parotid now T4	
Oral cavity	Lip SCC now staged under cutaneous carcinomas of HN	Uses the non-HPV, non-EBV nodal table
	Extrinsic muscle involvement no longer determines T4	
	DOI is new pathologic criterion for determining T status	

Note.—DOI = depth of invasion, EBV = Epstein-Barr virus, ENE = extranodal extension, HN = head and neck, HPV = human papilloma virus, SCC = squamous cell carcinoma.

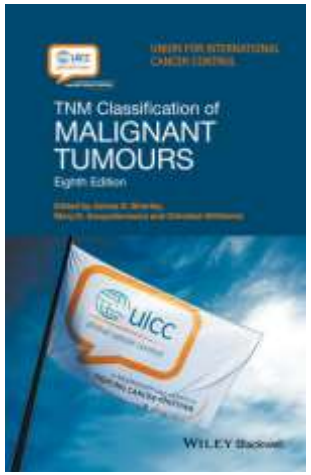
Table 2: Additional AJCC8 Changes to Head and Neck Cancer Staging

Tumor Type	Staging Changes
HPV-mediated oropharyngeal SCC	Marked change to prognostic groupings: N1 = stage I, N2 = stage II, N3 = stage III. Stage IV only if M1 disease
Unknown primary tumors	Part of new chapter on lymph nodes with new direction as to how to stage these tumors
	Directs pathologic evaluation of nodes to first determine whether p16 positive favoring HPV-mediated OPSCC
	No T category is assigned if node is HPV and EBV negative unless a skin primary site is clinically strongly favored
Cutaneous carcinoma of HN	New chapter and T category table for all skin lesions including lesions of the external dry lip (vermillion), but excluding eyelid tumors
Thyroid carcinoma	Thyroid-differentiated carcinoma chapter has been moved out of HN section to the Endocrine section of AJCC8
	For prognostic grouping to distinguish between stage I and stage II, the age has been changed from 45 years to 55 years
Soft-tissue sarcomas	New chapter in AJCC8 and is included in the Soft-Tissue Sarcoma section of AJCC8, not the HN section

Note.—AJCC = American Joint Committee on Cancer, EBV = Epstein-Barr virus, HN = head and neck, HPV = human papilloma virus, OPSCC = oropharyngeal squamous cell carcinoma, SCC = squamous cell carcinoma.

Glastonbury CM. Critical Changes in the Staging of Head and Neck Cancer. Radiol Imaging Cancer. 2020
TNM klasifikace zhoubných novotvarů. 8. vydání 2017, ÚZIS, Praha, 2018

HPV/p16 pozitivní karcinomy orofaryngu
Samostatná TNM klasifikace



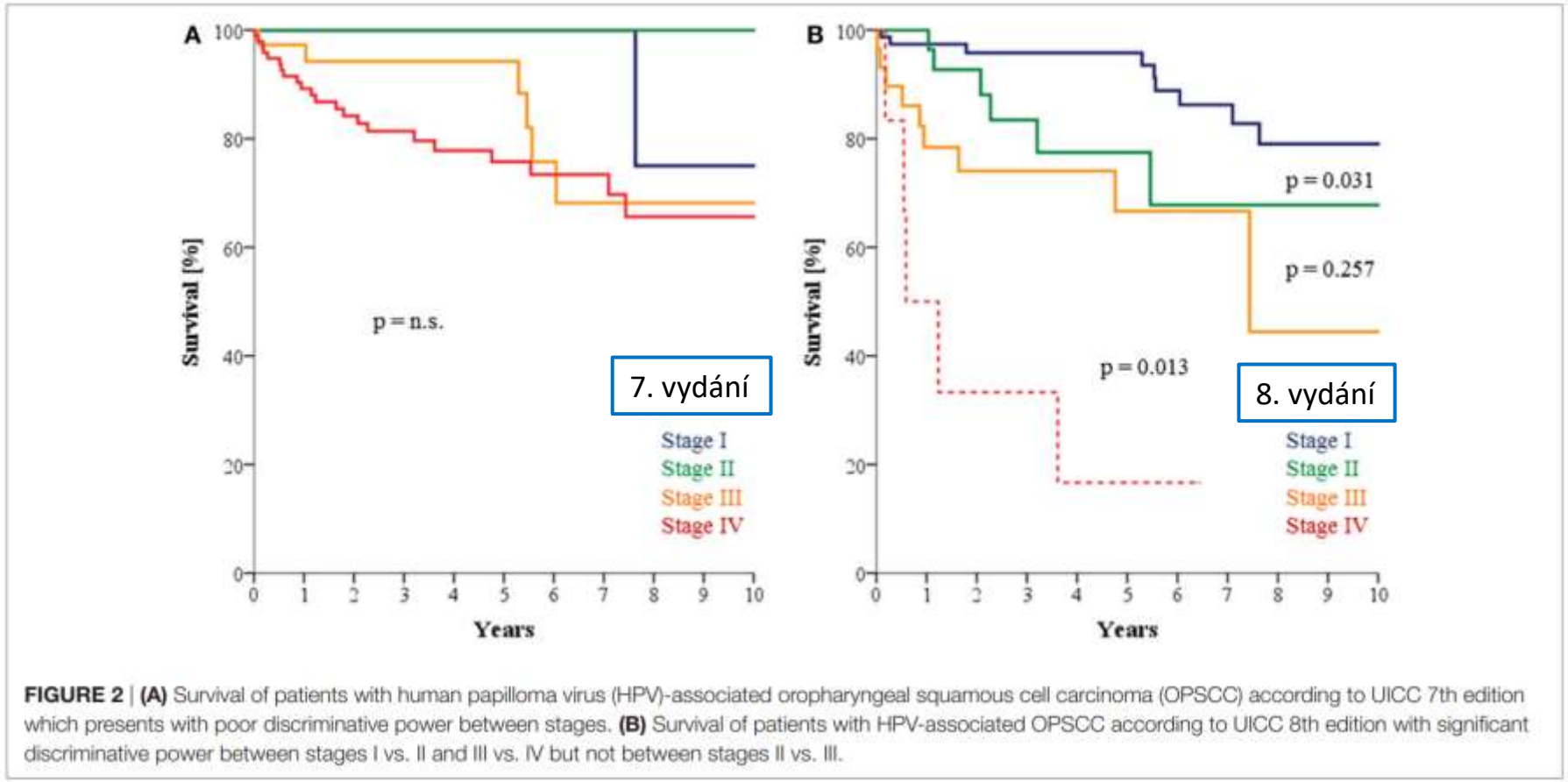


FIGURE 2 | **(A)** Survival of patients with human papilloma virus (HPV)-associated oropharyngeal squamous cell carcinoma (OPSCC) according to UICC 7th edition which presents with poor discriminative power between stages. **(B)** Survival of patients with HPV-associated OPSCC according to UICC 8th edition with significant discriminative power between stages I vs. II and III vs. IV but not between stages II vs. III.

Table 1: Critical Changes in

Tumor Type
Oropharyngeal SCC
HPV-related oropharyngeal
Non-HPV oropharyngeal S
Nasopharyngeal carcinoma
Oral cavity

Note.—DOI = depth of invasion, EBV = Epstein-Barr virus, ENE = extranodal extension, HN = head and neck, HPV = human papilloma virus, SCC = squamous cell carcinoma.

oupings: N1 = stage I, N2 = IV only if M1 disease
odes with new direction as to
nodes to first determine
; HPV-mediated OPSCC
le is HPV and EBV negative un-
ically strongly favored
le for all skin lesions includ-
lip (vermillion), but excluding
a chapter has been moved out
ne section of AJCC8
nguish between stage I and
nged from 45 years to 55 years
ncluded in the Soft-Tissue
Sarcoma section of AJCC8, not the HN section

Note.—AJCC = American Joint Committee on Cancer, EBV = Epstein-Barr virus, HN = head and neck, HPV = human papilloma virus, OPSCC = oropharyngeal squamous cell carcinoma, SCC = squamous cell carcinoma.

Glastonbury CM. Critical Changes in the Staging of Head and Neck Cancer. Radiol Imaging Cancer. 2020
TNM klasifikace zhoubných novotvarů. 8. vydání 2017, ÚZIS, Praha, 2018
Würdemann N, et al. Prognostic Impact of AJCC/UICC 8th Edition New Staging Rules in Oropharyngeal Squamous Cell Carcinoma. Front Oncol. 2017

Cetuximab vs. cDDP jako konkomitance s RT u lokálně pokročilých HPV+ karcinomů orofaryngu

„Deeskalace“?

	De-ESCALate HPV	RTOG 1018	TROG 12.01
Primary objective	Safety (toxicity reduction)	Survival (mOS)	Symptom severity
Design	Superiority	Non-inferiority	
Regimen	RT 70 Gy NF; CDDP 100mg/m2 á 3 týdny vs. cetuximab	RT 70 Gy/6 týdnů; CDDP 100mg/m2 á 3 týdny vs. cetuximab	RT 70 Gy NF; CDDP 40 mg/m2 týdně vs. cetuximab
Population	N=334 pts. Low risk – 100%	N=987 pts. Low risk – 71% Intermediate risk – 29%	N=189 pts. Low risk > 91% (modified inclusion criteria)
HPV tests used	p16 & HPV DNA	p16	P16 & HPV RNA
Median follow up	25.9 months	4.5 years	4.1 years

- *Mehanna H, et al: Radiotherapy plus cisplatin or cetuximab in low-risk human papillomavirus-positive oropharyngeal cancer (De-ESCALaTE HPV): An open-label randomised controlled phase 3 trial. Lancet 2019*
- *Gillison ML, et al. Radiotherapy plus cetuximab or cisplatin in human papillomavirus-positive oropharyngeal cancer (NRG Oncology RTOG 1016): a randomised, multicentre, non-inferiority trial. Lancet. 2019*
- *Rischin et al. Randomized Trial of Radiation Therapy With Weekly Cisplatin or Cetuximab in Low-Risk HPV Associated Oropharyngeal Cancer (TROG 12.01) – A Trans-Tasman Radiation Oncology Group StudyInt J Rad Oncol Biol Phys 2021*

De-ESCALATE HPV

N=334 pts.

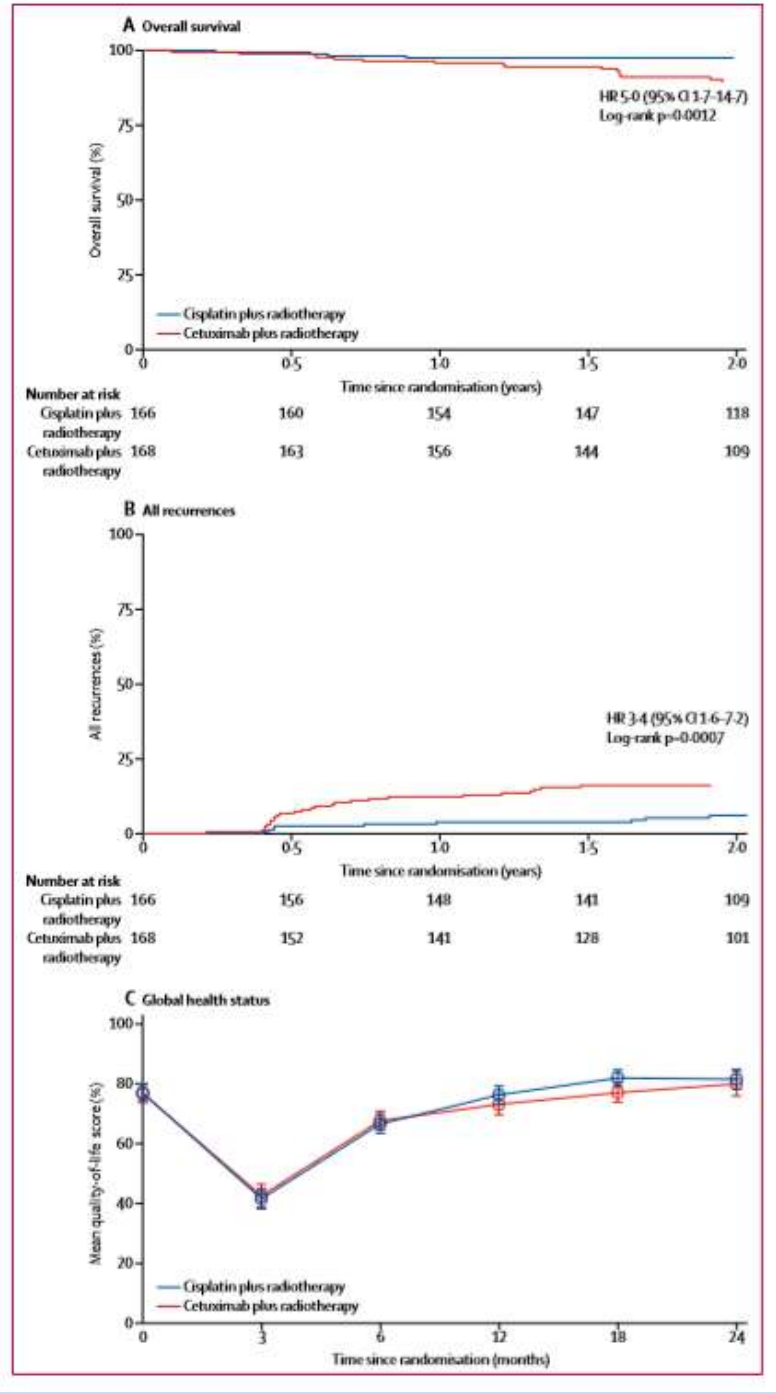
Karcinom orofaryngu p16+/HPV+
- Low risk (kouření < 10 PY)
- Intermediate stage (T3-T4 nebo N1-N3; M0)

Stratifikace:
centrum, T-stadium, N-stádium, lateralita RT, profylaktický PEG

R
1:1

RT 70 Gy NF + Cisplatina 100mg/m2 á 3 týdny

RT 70 Gy NF + Cetuximab 250 mg týdně (nasycovací dávka 400mg)



Mehanna H, et al: Radiotherapy plus cisplatin or cetuximab in low-risk human papillomavirus-positive oropharyngeal cancer (De-ESCALaTE HPV): An open-label randomised controlled phase 3 trial. Lancet 2019

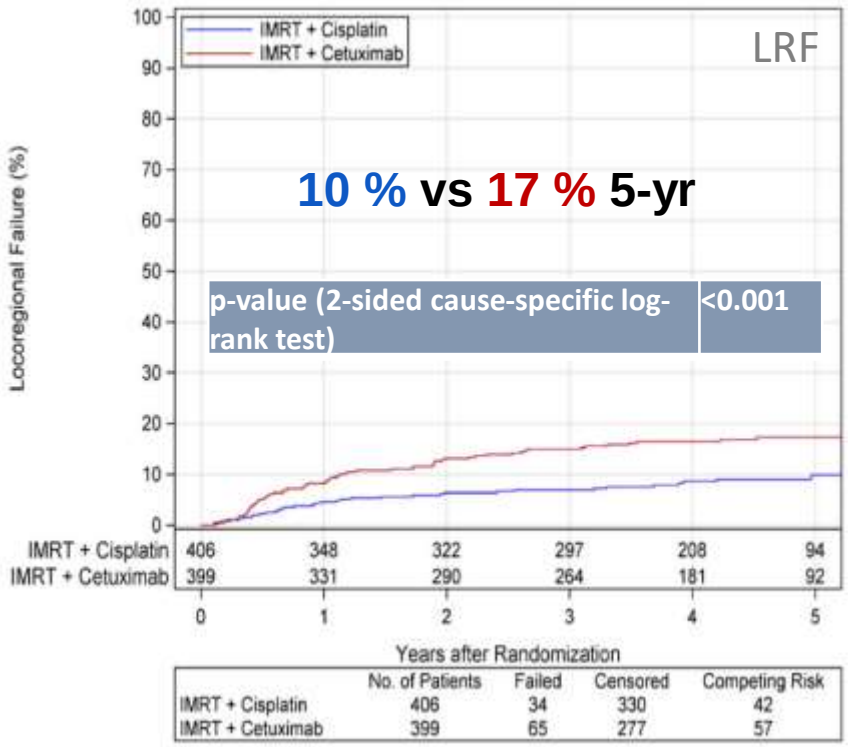
RTOG 1016

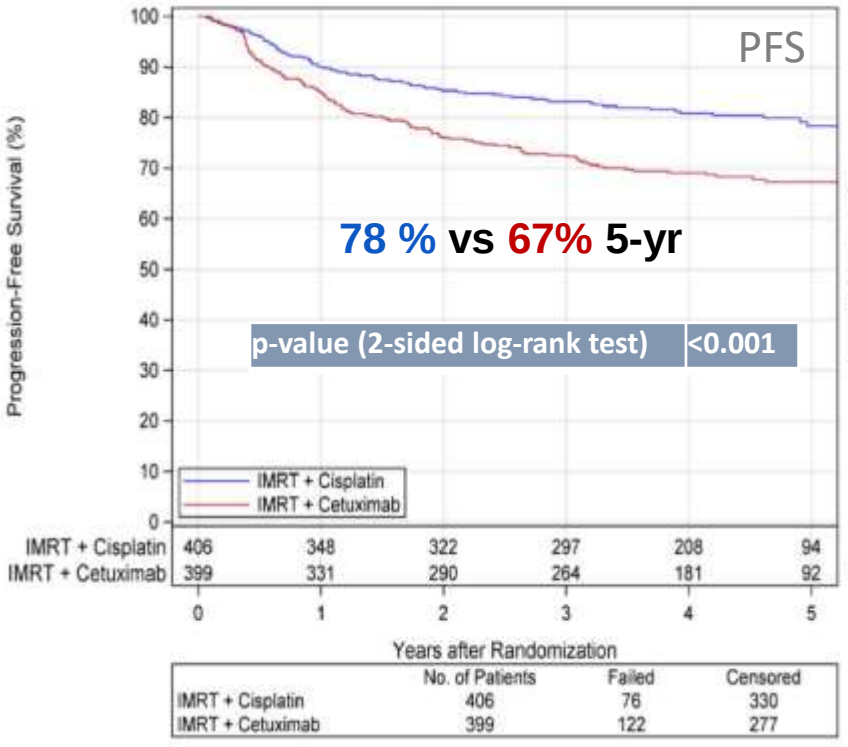
Phase III Trial of Radiotherapy plus Cetuximab versus Chemoradiotherapy in HPV-Related Oropharynx Cancer

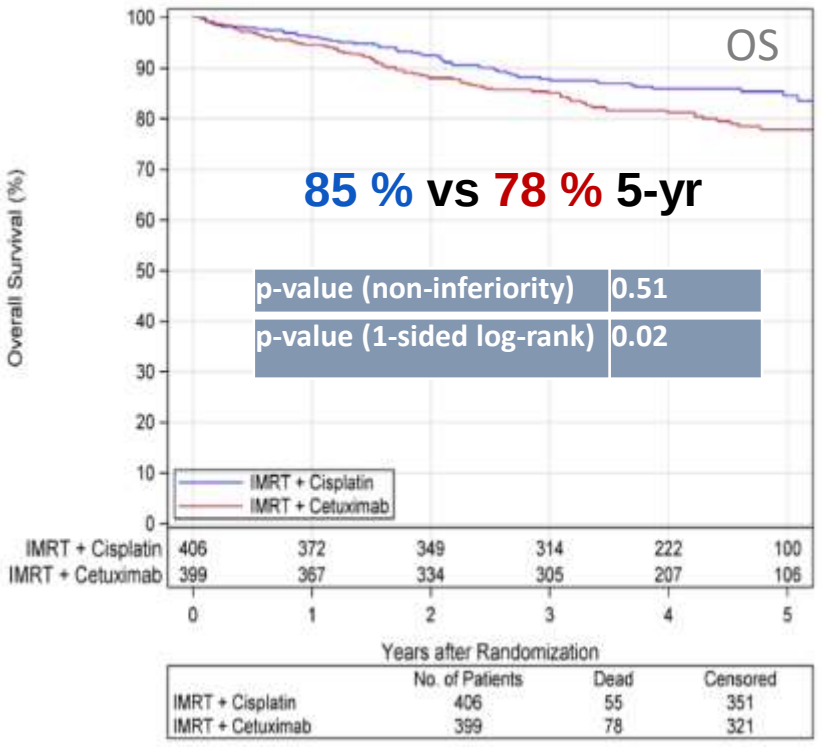
cisplatina vs cetuximab

N=987 pts.

RT 70 Gy/6 týdnů







Gillison ML, et al. Radiotherapy plus cetuximab or cisplatin in human papillomavirus-positive oropharyngeal cancer (NRG Oncology RTOG 1016): a randomised, multicentre, non-inferiority trial. Lancet. 2019

TROG 12.01

Karcinom orofaryngu p16+/HPV+
- Stádium III-IV
- Exlusion:
  - stádium T1-2N0-1
  - stádium T4 nebo N3
  - N2b-N2c (kouření > 10 PY)

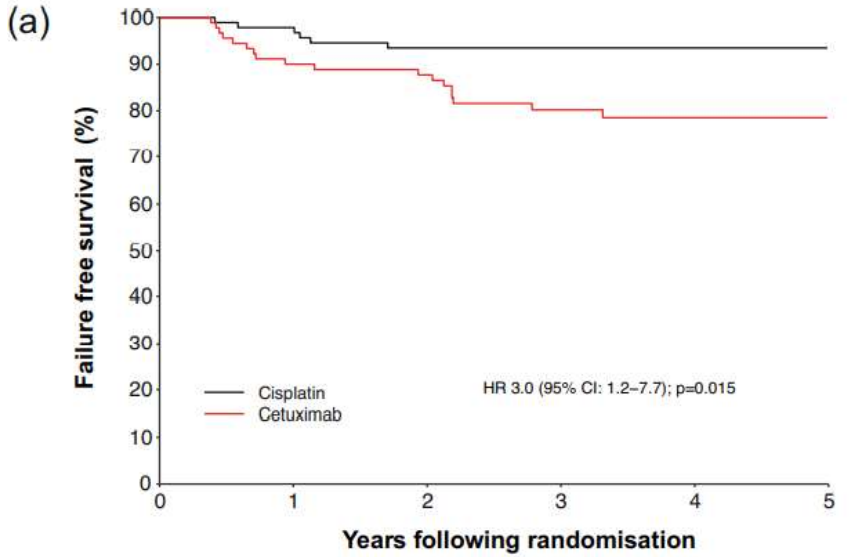
Stratifikace:
T-stadium, N-stádium, lateralita RT, centrum

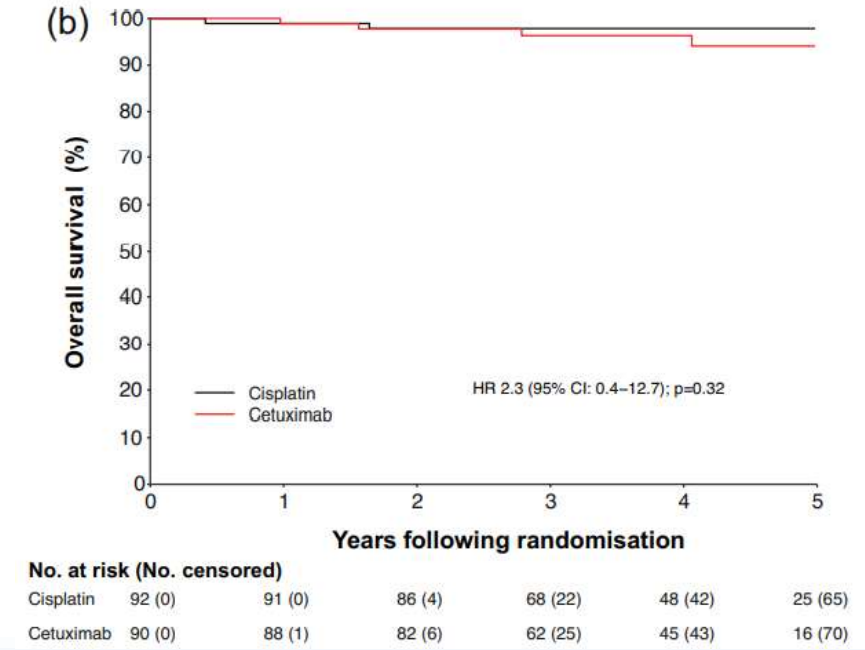
N=189 pts.

R 1:1

RT 70 Gy NF + Cisplatina 40 mg/m2 týdně

RT 70 Gy NF + Cetuximab 250 mg týdně (nasycovací dávka 400mg)





Rischin et al. Randomized Trial of Radiation Therapy With Weekly Cisplatin or Cetuximab in Low-Risk HPV Associated Oropharyngeal Cancer (TROG 12.01) − A Trans-Tasman Radiation Oncology Group Study Int J Rad Oncol Biol Phys 2021

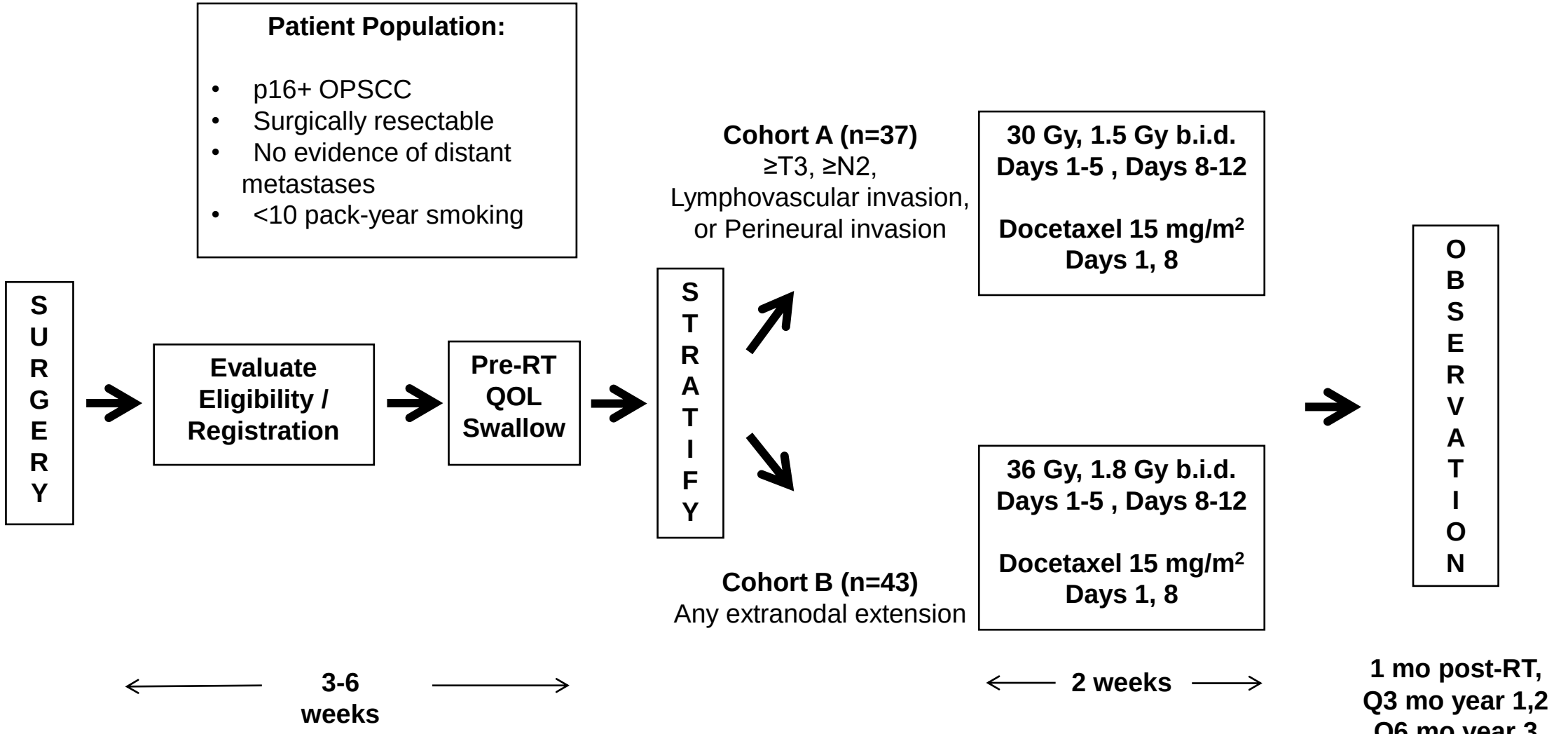
TROG 12.01

Karcinom orofaryngu p1
- Stádium III-IV
- Exlusion:
  - stádium T1-2N
  - stádium T4 ne
  - N2b-N2c (kou

Stratifikace:
T-stadium, N-stádium, la
centrum

Rischin et al. Randomized Trial of Radiation Therapy With Weekly Cisplatin or Cetuximab in Low-Risk HPV Associated Oropharyngeal Cancer (TROG 12.01) − A Trans-Tasman Radiation Oncology Group Study Int J Rad Oncol Biol Phys 2021

MC1273, A Phase II Evaluation of De-escalated Adjuvant RT for HPV+ Oropharyngeal SCC

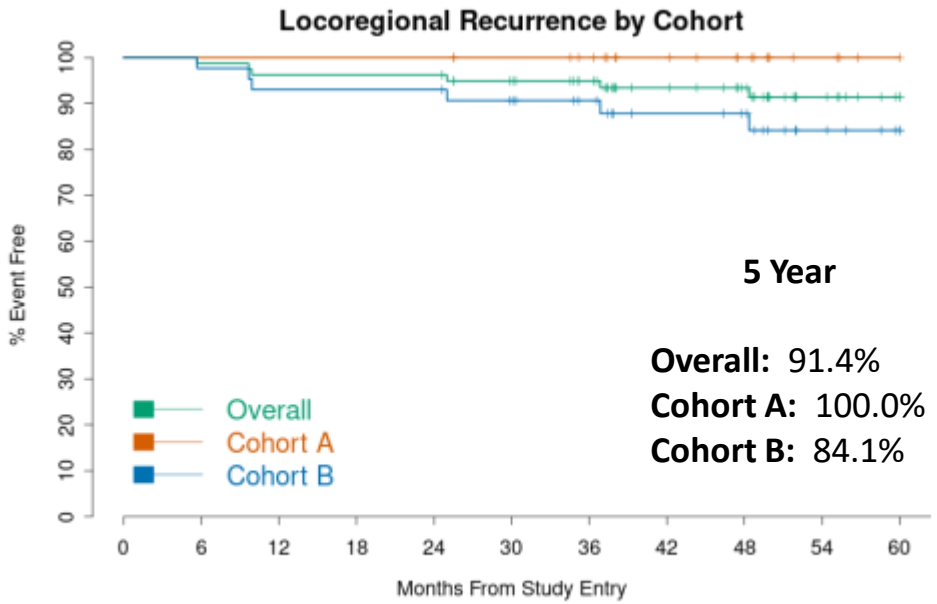


Ma DJ, et al. ASTRO 2021

MC1273
A Phase II Evaluation of De-escalated Adjuvant RT for HPV+ Oropharyngeal SCC

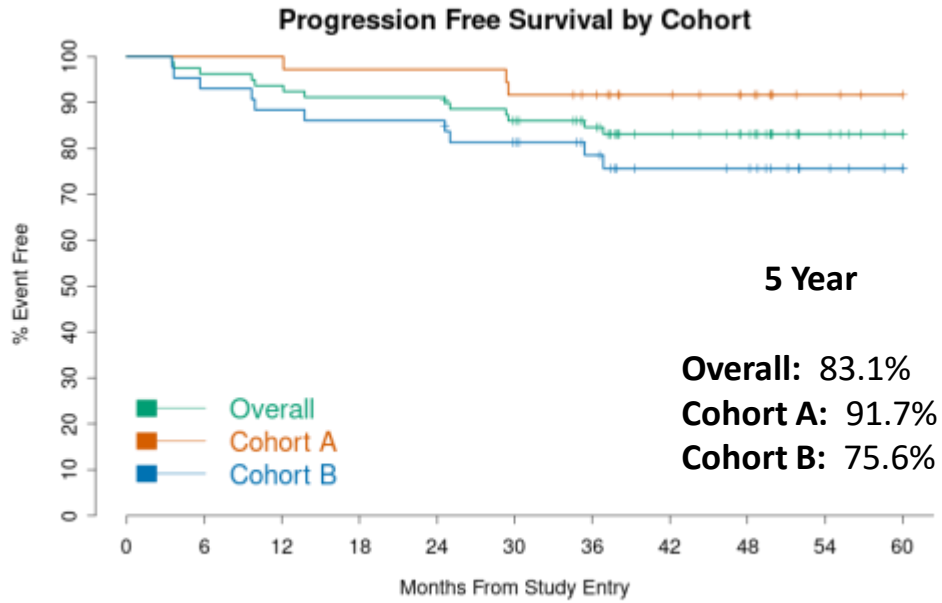
Cohort A (n=37) ≥T3, ≥N2, LVI or PNI

Cohort B (n=43): Any extranodal extension



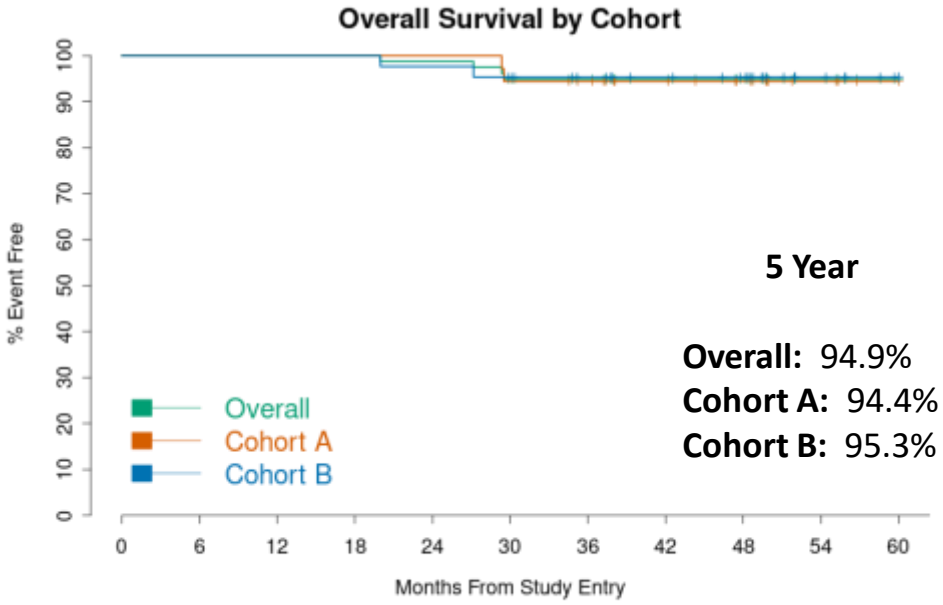
5 Year

Overall: 91.4%
Cohort A: 100.0%
Cohort B: 84.1%



5 Year

Overall: 83.1%
Cohort A: 91.7%
Cohort B: 75.6%

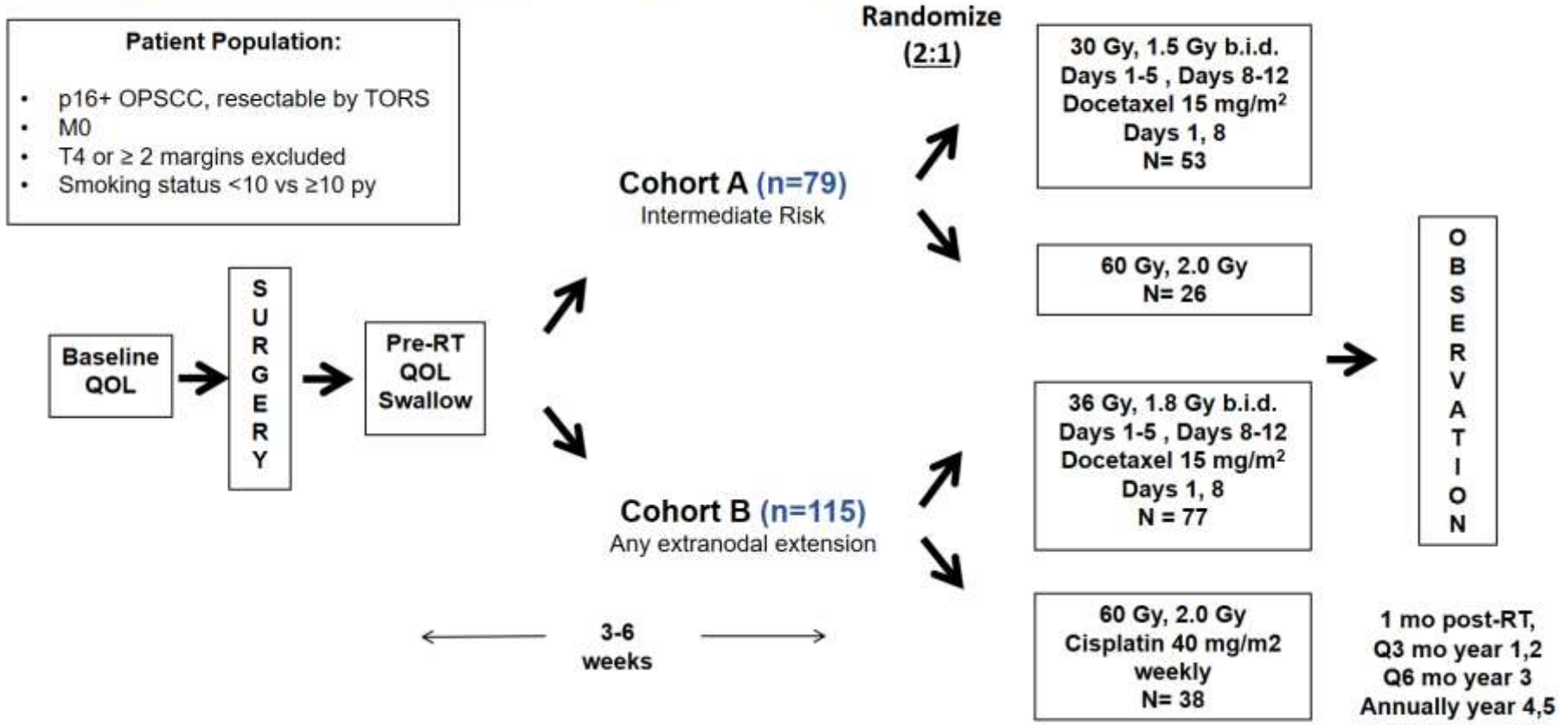


5 Year

Overall: 94.9%
Cohort A: 94.4%
Cohort B: 95.3%

Ma DJ, et al. ASTRO 2021

Background: MC1675 (DART)



Ma DJ, et al. ASTRO 2021

Background: MC1675 (DART)

Patient Population:

- p16+ OPSCC, resecta
- M0
- T4 or ≥ 2 margins exc
- Smoking status <10 v

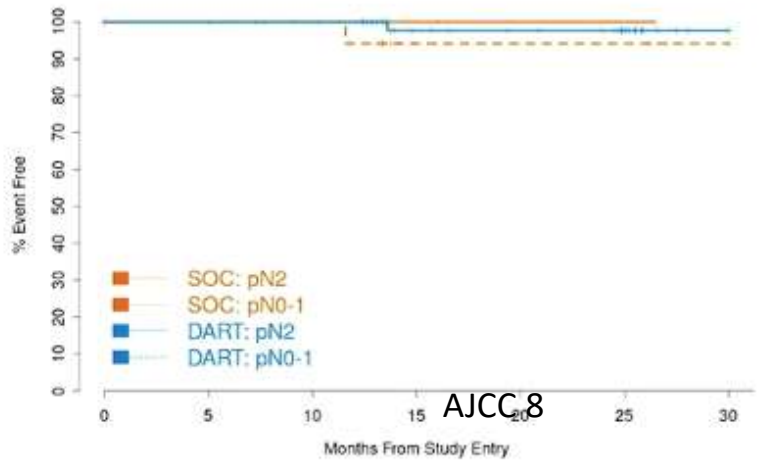
Randomize (2:1)

30 Gy, 1.5 Gy b.i.d. Days 1-5, Days 8-12

Baseline QOL → **SURGERY**

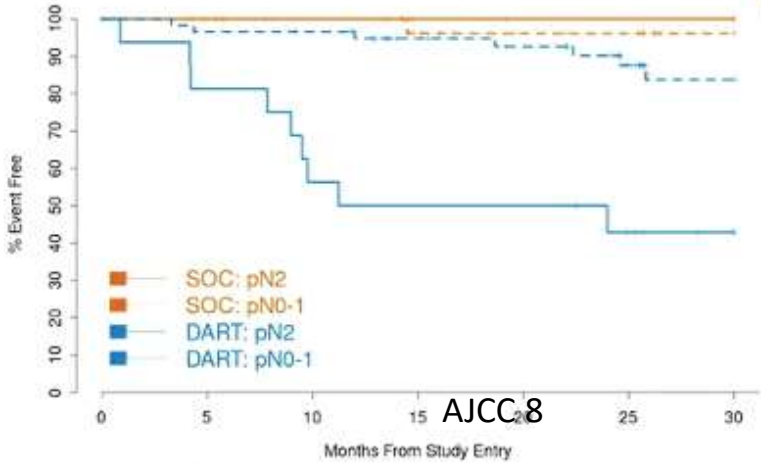
Results: Progression Free Survival

ENE-



AJCC 8

ENE+



AJCC 8

PFS	DMFS	LRC
SOC pN2: 100%	SOC pN2: 100%	SOC pN2: 100%
DART pN2: 42.9%	DART pN2: 59.4%	DART pN2: 77.0%

STAY CONNECTED #ASTRO21

Ma DJ, et al. ASTRO 2021

A Phase 2 Trial of Alternative Volumes of Oropharyngeal Irradiation for De-intensification (AVOID): Omission of the resected primary tumor bed after TORS for HPV+ SCC of the oropharynx

The trial enrolled 60 patients after TORS and selective ND (2014-2017) for pT1-pT2 N1-3 HPV+ OPSCC

- favorable features at the primary site: negative surgical margins ≥2 mm, no PNI, no LVI
- required adjuvant RT based on lymph node involvement.

Patients received postoperative RT to at-risk areas in the involved neck (60-66 Gy) and uninvolved neck (54 Gy).

- The resected primary site was treated as an active avoidance structure in the treatment planning of postoperative RT.
- Concurrent chemotherapy was administered for patients with extranodal extension.

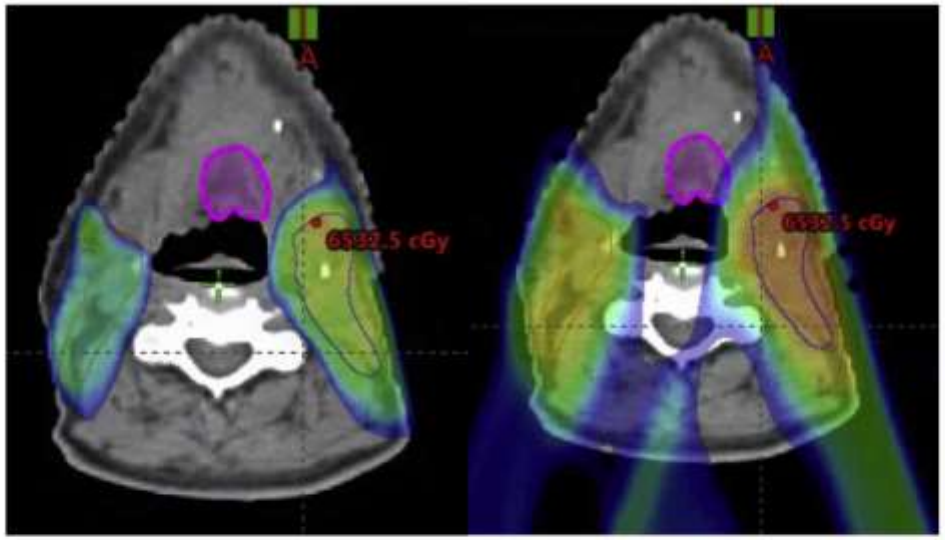


Fig. 2. Illustrative example radiation treatment plan: study patient with a pT1N2a (American Joint Committee on Cancer seventh edition) p16+ squamous cell carcinoma arising from the left base of the tongue. The primary site operative bed is shown in violet. The left neck is clinical target volume 6000 and right neck is clinical target volume 5000. The measured mean dose to the operative bed is 14 Gy. Dose color wash set at 50 Gy (left) and 20 Gy (right). (A color version of this figure is available at https://doi.org/10.1016/j.ijrobp.2019.11.021).

International Journal of Radiation Oncology biology • physics
www.redjournal.org

Clinical Investigation

A Phase 2 Trial of Alternative Volumes of Oropharyngeal Irradiation for De-intensification (AVOID): Omission of the Resected Primary Tumor Bed After Transoral Robotic Surgery for Human Papilloma Virus–Related Squamous Cell Carcinoma of the Oropharynx

Samuel Swisher-McClure, MD,* John N. Lukens, MD,* Charu Aggarwal, MD,† Peter Ahn, MD,* Devraj Basu, MD, PhD,‡ Joshua M. Bauml, MD,† Robert Brody, MD,‡ Ara Chalian, MD,‡ Roger B. Cohen, MD,† Alireza Fotouhi-Ghiam, MD,* Geoffrey Geiger, MD,* Jared Gershowitz, BS,* Virginia Livolsi, MD,§ Nandita Mitra, PhD,‖ Kathleen Montone, MD,§ Jason Newman, MD,‡ Eric Ojerholm, MD,* Bert O'Malley, Jr, MD,‡ Karthik Rajasekaran, MD,‡ Erik Tan, BS,* Gregory Weinstein, MD,‡ and Alexander Lin, MD*

*Departments of *Radiation Oncology, †Medicine, Division of Hematology/Oncology, ‡Otorhinolaryngology, §Pathology and Laboratory Medicine, and ‖Biostatistics, Epidemiology, and Informatics, University of Pennsylvania, Philadelphia, Pennsylvania*

Received Aug 23, 2019. Accepted for publication Nov 1, 2019.

Summary

Approaches to decrease treatment-related toxicity are needed for patients with HPV-associated oropharynx cancer. This study reports on

Purpose: This trial tested the safety and efficacy of a novel, deintensified radiation therapy (RT) approach after initial surgical resection for patients with human papilloma virus (HPV)-associated oropharyngeal squamous cell carcinoma (OPSCC).
Methods and Materials: This single-arm phase 2 prospective clinical trial enrolled 60 patients with stage pT1-pT2 N1-3 HPV-associated OPSCC treated with transoral robotic surgery (TORS) and selective neck dissection at a single institution between

Corresponding author: Alexander Lin, MD; E-mail: Alexander.Lin@uphs.upenn.edu

Samuel Swisher-McClure and John N. Lukens made equal contributions to this study.

This study was supported by a Pilot Research Grant awarded through the Department of Radiation Oncology, University of Pennsylvania Perelman School of Medicine.

Disclosures: G.W. and B.O. serve as paid consultants for Olympus medical. J.N. serves as a paid consultant for Medtronic, Castle Biosciences, and Just Right Surgical. C.A. serves on advisory boards for Bristol Myers Squibb, Celgene, Roche, Genentech, and Astra Zeneca. J.M.B. reports grants and personal fees from Merck, grants and personal fees from Clovis, grants from Carevive Systems, grants from Novartis, grants from Bayer, grants and personal fees from Janssen, grants and personal fees from Astra Zeneca, grants and personal fees from Takeda, personal fees from BMS, personal fees from Celgene, personal fees from Boehringer Ingelheim, personal fees from Guardant Health, and personal fees from Genentech.

Int J Radiation Oncol Biol Phys, Vol. 106, No. 4, pp. 725–732, 2020
0360-3016/$ - see front matter
https://doi.org/10.1016/j.ijrobp.2019.11.021

A Phase 2 Trial of Alternative Volumes of Oropharyngeal Irradiation for De-intensification (AVOID): Omission of the resected primary tumor bed after TORS for HPV+ SCC of the oropharynx

The trial enrolled 60 patien[illegible] after TORS and selective ND (2014-2017) for pT1-pT2 N1-2 HPV+ OPSCC

- favorable features at th
- required adjuvant RT ba

Patients received postoper[illegible] uninvolved neck (54 Gy).

- The resected primary si[illegible] planning of postoperati
- Concurrent chemothera

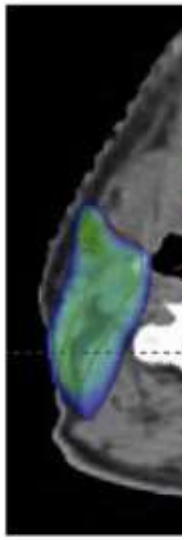


Fig. 2. Illustrative example rad[illegible] seventh edition) p16+ squamous[illegible] shown in violet. The left neck is[illegible] mean dose to the operative bed is[illegible] is available at https://doi.org/10.1016/j.ijrobp.2019.11.021).

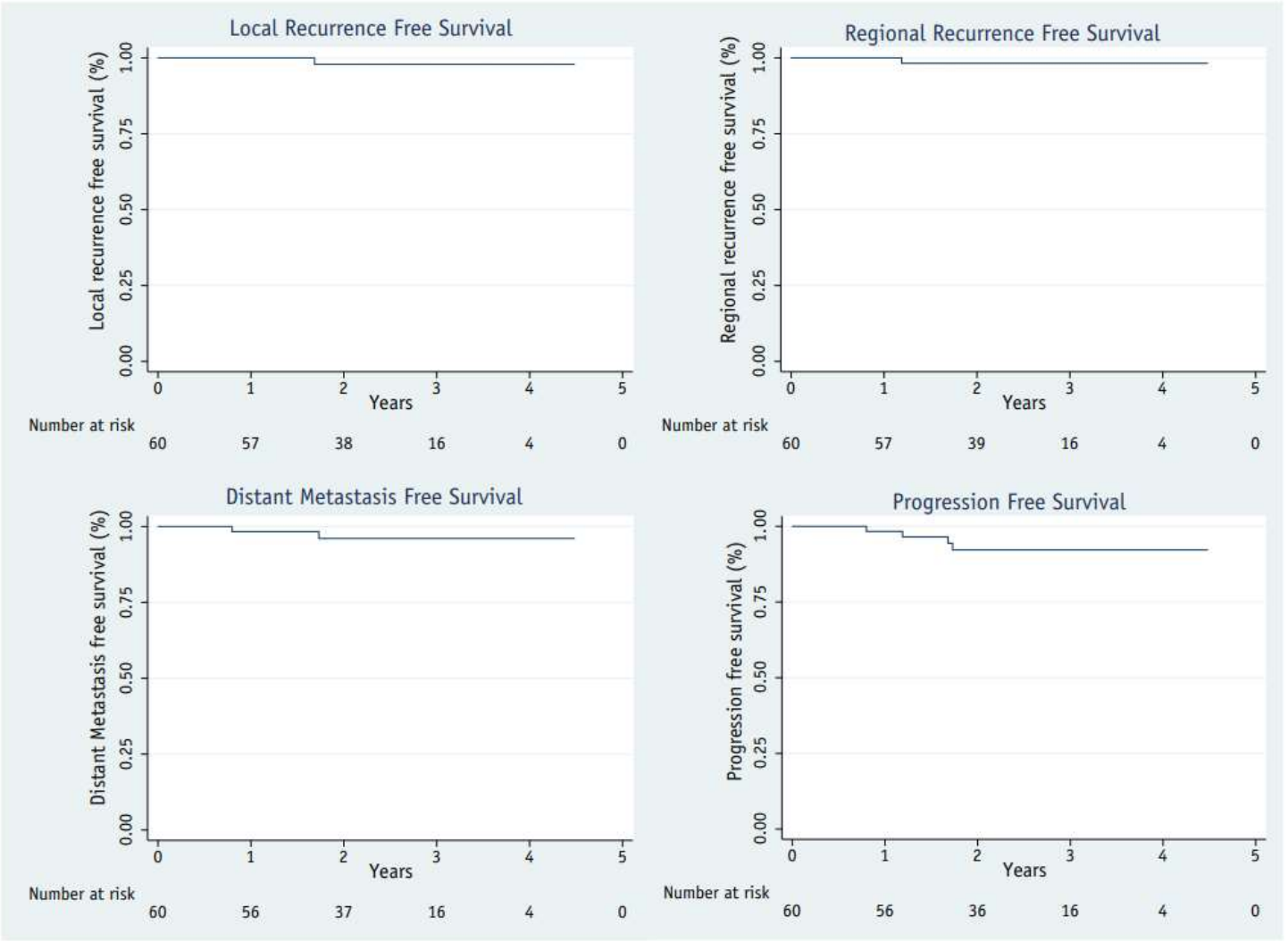


Fig. 4. Kaplan-Meier curves of local recurrence–free survival, regional recurrence–free survival, distant metastasis–free survival, and progression-free survival.

International Journal of Radiation Oncology biology • physics
www.redjournal.org

[illegible]ernative Volumes of [illegible]ation for De-intensification [illegible]f the Resected Primary [illegible]soral Robotic Surgery for [illegible]us–Related Squamous Cell [illegible]pharynx

[illegible] John N. Lukens, MD,* [illegible]n, MD,* Devraj Basu, MD, PhD,† [illegible] Brody, MD,† Ara Chalian, MD,† [illegible]otouhi-Ghiam, MD,* [illegible]ershowitz, BS,* Virginia Livolsi, MD,§ [illegible] Montone, MD,§ Jason Newman, MD,† [illegible]lley, Jr, MD,† Karthik Rajasekaran, MD,† [illegible]ein, MD,† and Alexander Lin, MD*

[illegible]icine, Division of Hematology/Oncology, [illegible]ratory Medicine, and †Biostatistics, Epidemiology, and [illegible]iladelphia, Pennsylvania

Nov 1, 2019.

[illegible]e: This trial tested the safety and efficacy of a novel, deintensified radiation [illegible] (RT) approach after initial surgical resection for patients with human papil-[illegible]irus (HPV)-associated oropharyngeal squamous cell carcinoma (OPSCC).

[illegible]ds and Materials: This single-arm phase 2 prospective clinical trial enrolled 60 [illegible]s with stage pT1-pT2 N1-3 HPV-associated OPSCC treated with transoral ro-[illegible]urgery (TORS) and selective neck dissection at a single institution between

[illegible]Alexander.Lin@

[illegible]e equal contribu-

[illegible]awarded through [illegible]Pennsylvania Per-

[illegible]nts for Olympus [illegible]leltronic, Castle

Biosciences, and Just Right Surgical. C.A. serves on advisory boards for Bristol Myers Squibb, Celgene, Roche, Genentech, and Astra Zeneca. J.M.B. reports grants and personal fees from Merck, grants and personal fees from Clovis, grants from Carevive Systems, grants from Novartis, grants from Bayer, grants and personal fees from Janssen, grants and personal fees from Astra Zeneca, grants and personal fees from Takeda, personal fees from BMS, personal fees from Celgene, personal fees from Boehringer Ingelheim, personal fees from Guardant Health, and personal fees from Genentech.

[illegible]25–732, 2020

Take home message #1

- Narůstá relativní i absolutní počet HPV+ karcinomů orofaryngu
- HPV+ nádory jsou spojeny s významně lepší prognózou
- Cílem deeskalačních studií je snížit riziko pozdních následků léčby
- Data dosud nejsou dostatečná, proto HPV status nelze pokládat prediktor léčby

… pokračování

Take home message #1

- Status HPV/p16 je možné spolu s dalšími rizikovými faktory využít pro rozhodování o strategii léčby v rámci mezioborových týmů

Režimy systémové protinádorové léčby R/M SCCHN

Paliativní chemoterapie:

- Monochemoterapie (cDDP, CBDCA, MTX…)
- Polychemoterapie (cDDP-FU)

  Medián přežití: bez CHT 4-6 měsíců

  s CHT 6-8 měsíců

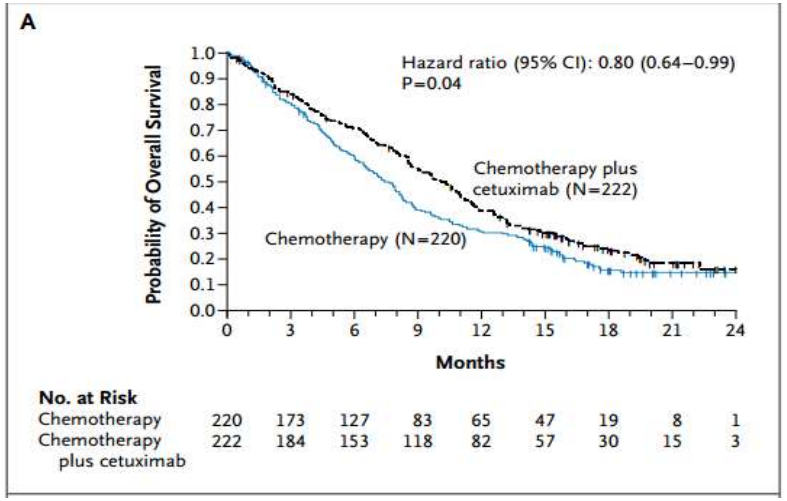
Regimen	ORR, %	Median survival, months
Cisplatin + 5-fluorouracil[1–4]	30–32	5.5–8.7
Cisplatin[1,3]	15–17	5.0–6.7
5-fluorouracil[1]	13	6.1
Carboplatin + 5-fluorouracil[2]	21	5.0
Methotrexate[2]	10	5.6
Cisplatin, methotrexate, bleomycin, vincristine[3]	34	7.0
Cisplatin + paclitaxel[4]	26	8.1

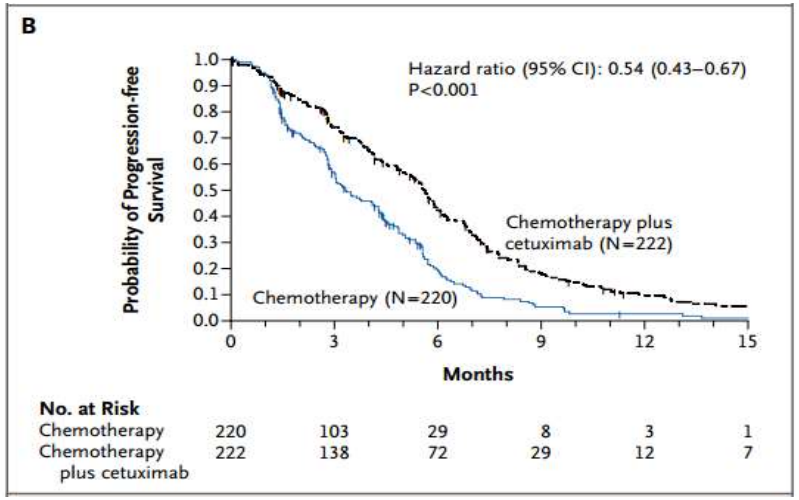
Studie EXTREME:

cDDP(CBDCA)-FU + cetuximab

vs. cDDP(CBDCA)-FU

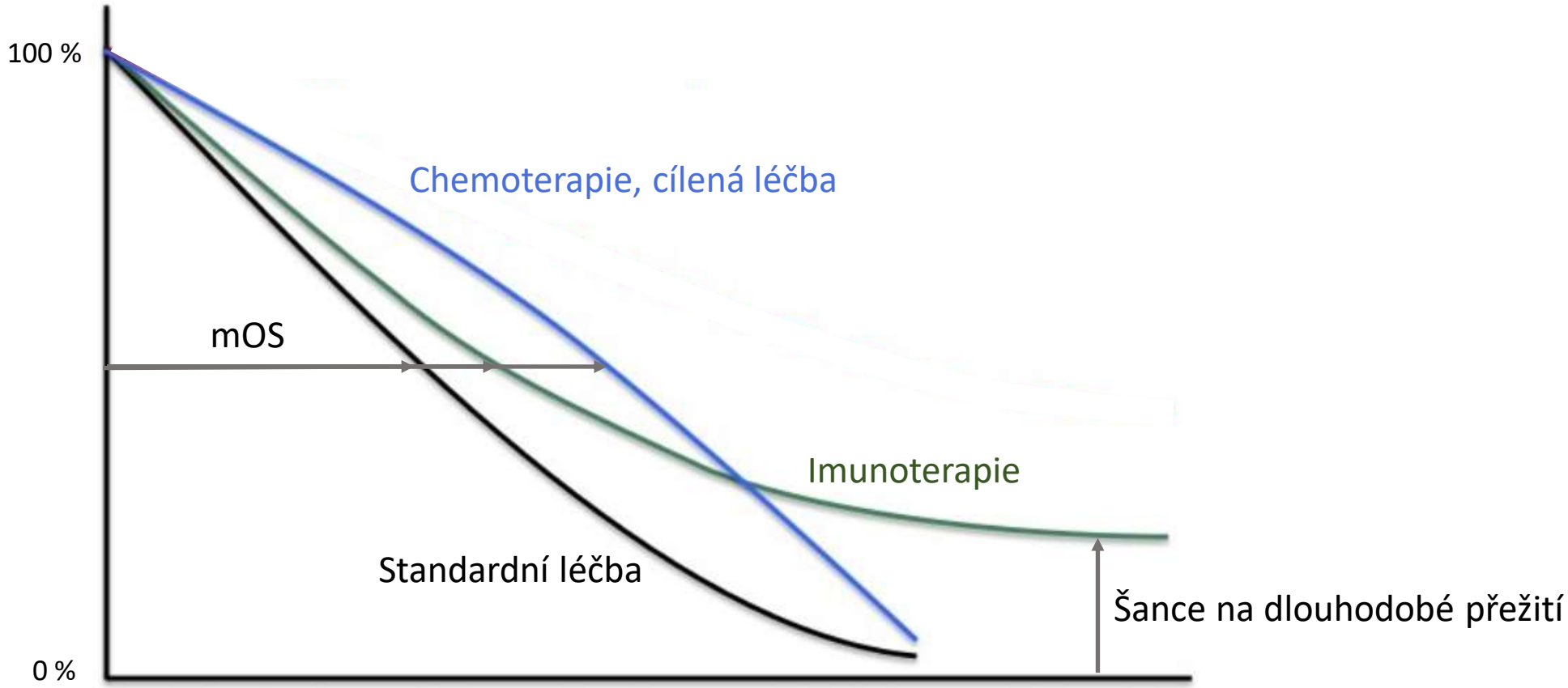
mOS - 10,1 měsíce vs. 7,4 měsíce





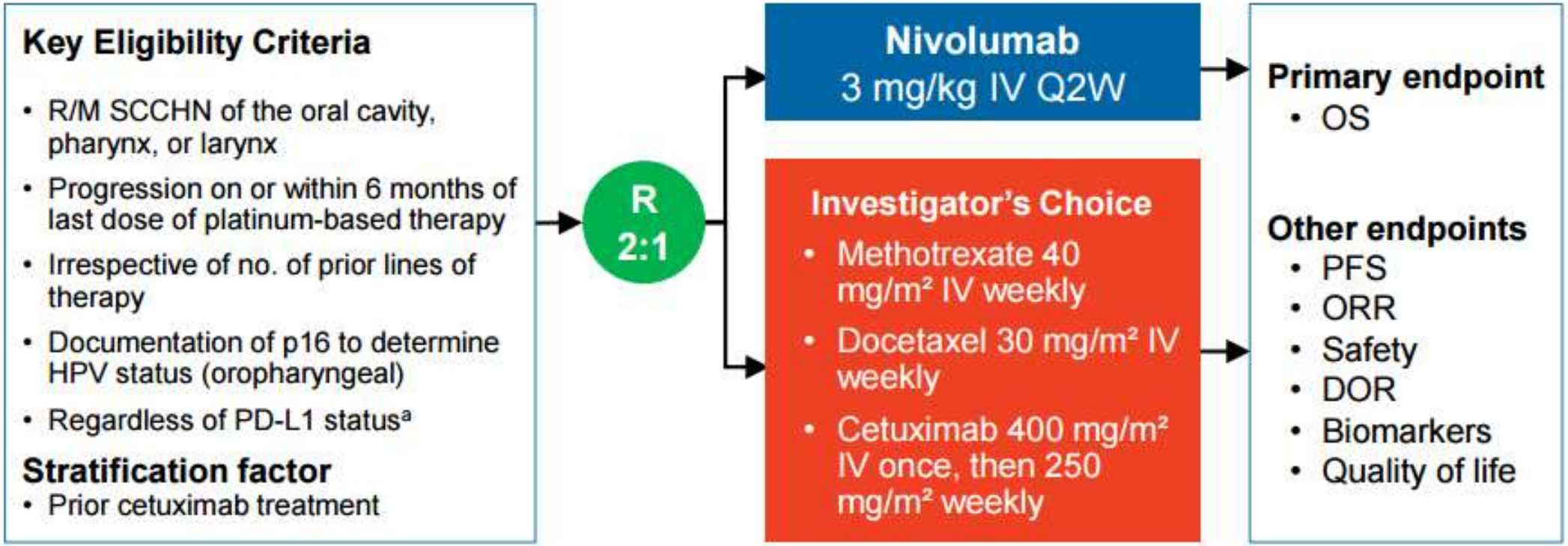
- *Jacobs C et al J Clin Oncol 1992*
- *Forastiere AA et al J Clin Oncol 1992*
- *Clavel M et al. Ann Ocol 1994*
- *Gibson MK et al J Clin Oncol 2005*
- *Vermorken et al. NEJM 2008*

Kaplan-Meierovy křivky celkového přežití rekurentních a metastatických nádorů



Phase 3 CheckMate 141 Study Design
Nivolumab in R/M SCCHN After Platinum Therapy

- Randomized, global, phase 3 trial of the efficacy and safety of nivolumab vs investigator's choice in patients with R/M SCCHN



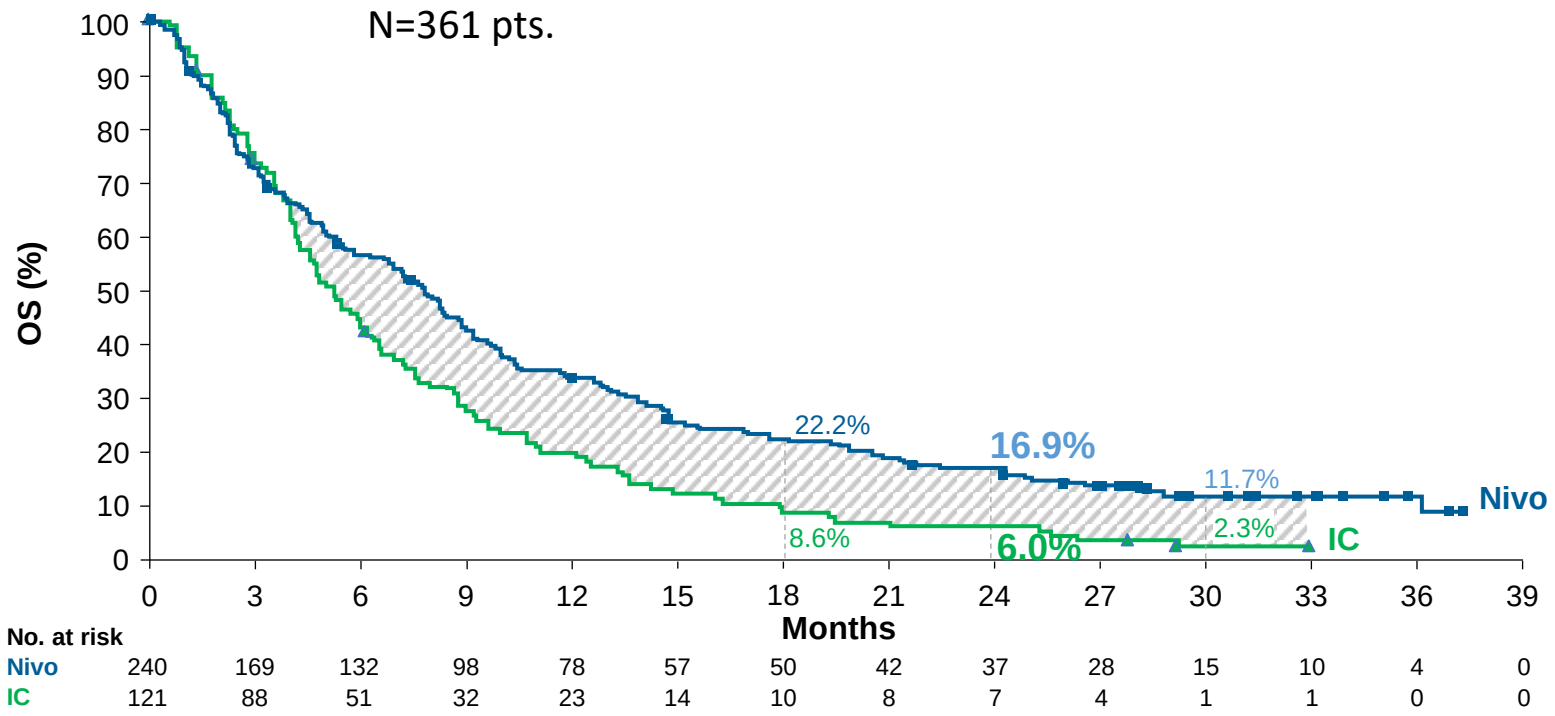
[a]Tissue required for testing.

DOR = duration of response; IV = intravenous; ORR = objective response rate; PFS = progression-free survival; Q2W = once every 2 weeks; R = randomized.
Clinicaltrials.gov NCT02105636.

Ferris et al. ASCO 2016

CheckMate 141 - OS Benefit in the Overall (ITT) Population

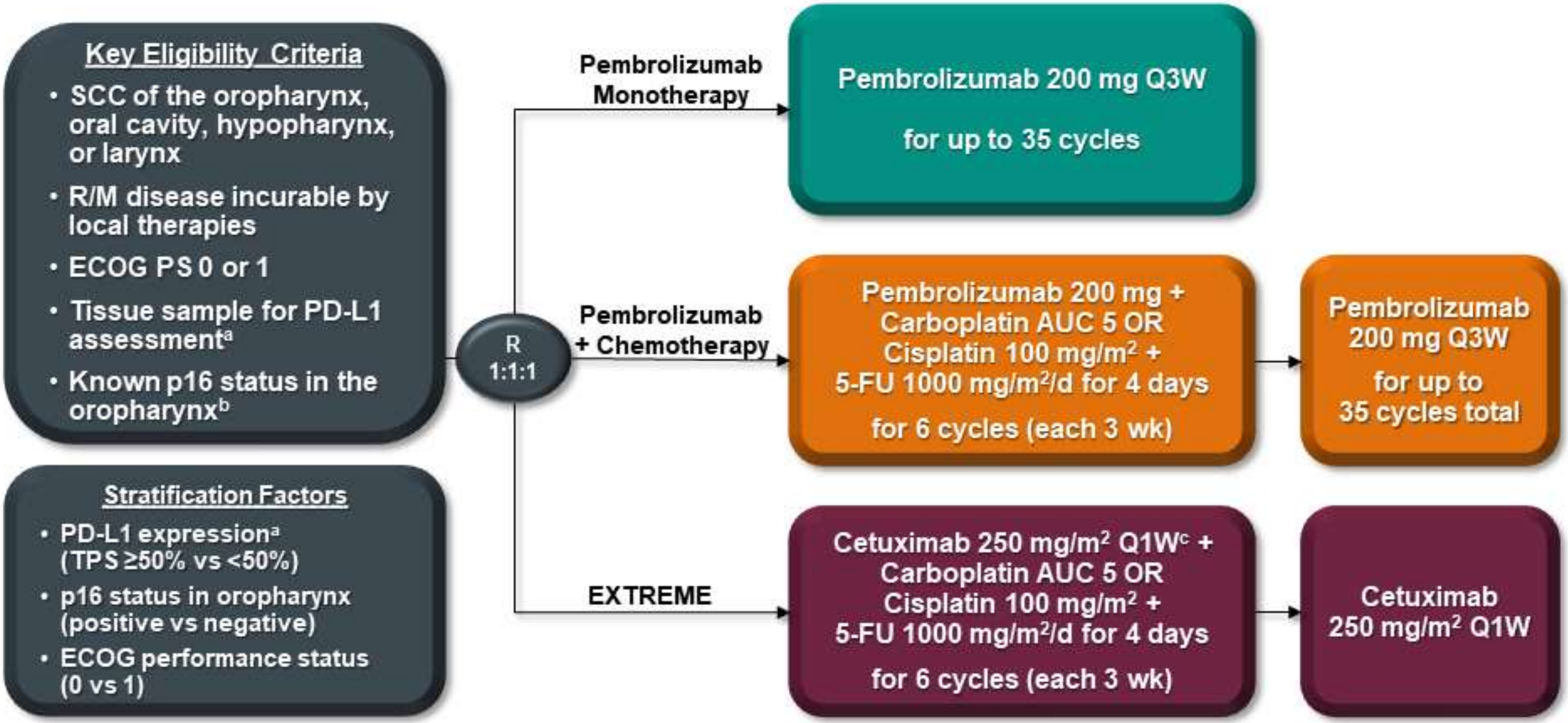
- Nivolumab reduced the risk of death by 32% vs IC
- The 24-month OS rate was nearly tripled with nivolumab compared with IC



Symbols represent censored observations. ITT = intent-to-treat; Nivo, nivolumab

Ferris et al., AACR 2018

KEYNOTE-048 Study Design (NCT02358031)



[a]Assessed using the PD-L1 IHC 22C3 pharmDx assay (Agilent). TPS = tumor proportion score = % of tumor cells with membranous PD-L1 expression. [b]Assessed using the CINtec p16 Histology assay (Ventana); cutpoint for positivity = 70%. [c]Following a loading dose of 400 mg/m².

KEYNOTE-048 Study Design (NCT02358031)

Key Eligibility Criteria

- SCC of the oropharynx, oral cavity, hypopharynx, or larynx
- R/M disease incurable by local therapies
- ECOG PS 0 or 1
- Tissue sample for PD-L1 assessment[a]
- Known p16 status in the oropharynx[b]

Stratification Factors

- PD-L1 expression[a] (TPS ≥50% vs <50%)
- p16 status in oropharynx (positive vs negative)
- ECOG performance status (0 vs 1)

R 1:1:1

Pembrolizumab Monotherapy → Pembrolizumab 200 mg Q3W for up to 35 cycles

Pembrolizumab + Chemotherapy → Pembrolizumab 200 mg + Carboplatin AUC 5 OR Cisplatin 100 mg/m² + 5-FU 1000 mg/m²/d for 4 days for 6 cycles (each 3 wk) → Pembrolizumab 200 mg Q3W for up to 35 cycles total

EXTREME → Cetuximab 250 mg/m² Q1W[c] + Carboplatin AUC 5 OR Cisplatin 100 mg/m² + 5-FU 1000 mg/m²/d for 4 days for 6 cycles (each 3 wk) → Cetuximab 250 mg/m² Q1W

[a]Assessed using the PD-L1 IHC 22C3 pharmDx assay (Agilent). TPS = tumor proportion score = % of tumor cells with membranous PD-L1 expression.
[b]Assessed using the CINtec p16 Histology assay (Ventana); cutpoint for positivity = 70%. [c]Following a loading dose of 400 mg/m².

KEYNOTE-048 Study Design (NCT02358031)

Key Eligibility Criteria

- SCC of the oropharynx, oral cavity, hypopharynx, or larynx
- R/M disease incurable by local therapies
- ECOG PS 0 or 1
- Tissue sample for PD-L1 assessment[a]
- Known p16 status in the oropharynx[b]

Stratification Factors

- PD-L1 expression[a] (TPS ≥50% vs <50%)
- p16 status in oropharynx (positive vs negative)
- ECOG performance status (0 vs 1)

R 1:1:1

Pembrolizumab Monotherapy → Pembrolizumab 200 mg Q3W for up to 35 cycles

Pembrolizumab + Chemotherapy → Pembrolizumab 200 mg + Carboplatin AUC 5 OR Cisplatin 100 mg/m² + 5-FU 1000 mg/m²/d for 4 days for 6 cycles (each 3 wk) → Pembrolizumab 200 mg Q3W for up to 35 cycles total

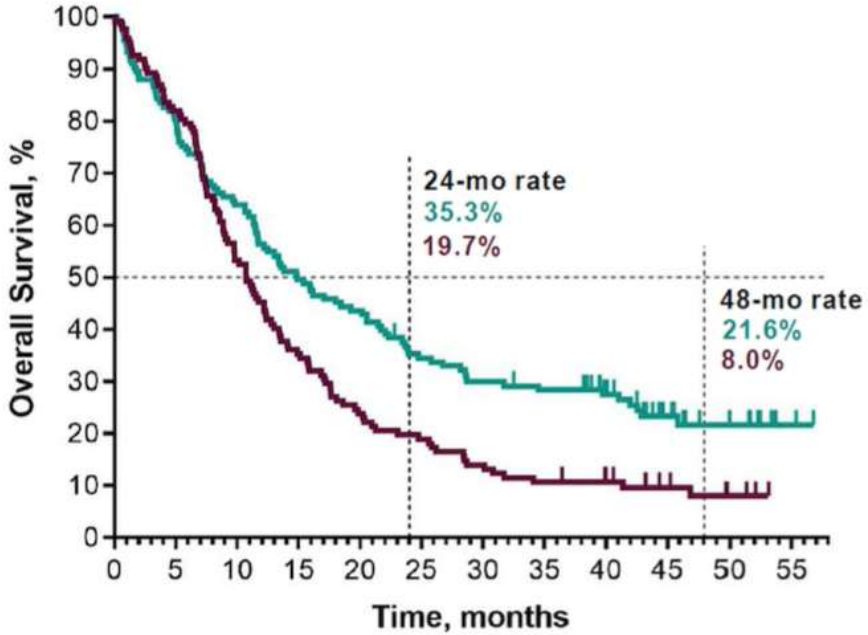
EXTREME → Cetuximab 250 mg/m² Q1W[c] + Carboplatin AUC 5 OR Cisplatin 100 mg/m² + 5-FU 1000 mg/m²/d for 4 days for 6 cycles (each 3 wk) → Cetuximab 250 mg/m² Q1W

[a]Assessed using the PD-L1 IHC 22C3 pharmDx assay (Agilent). TPS = tumor proportion score of tumor cells with membranous PD-L1 expression.
[b]Assessed using the CINtec p16 Histology assay (Ventana); cutpoint for positivity = 70%. [c]Following a loading dose of 400 mg/m².

4-Year OS: Pembrolizumab vs EXTREME

PD-L1 CPS ≥20

	Events	Median OS, mo (95% CI)	HR (95% CI)	*P* value[a]
Pembrolizumab	75.9%	14.9 (11.5-20.6)	0.61 (0.46-0.81)	0.00034
EXTREME	91.0%	10.8 (8.8-12.8)		

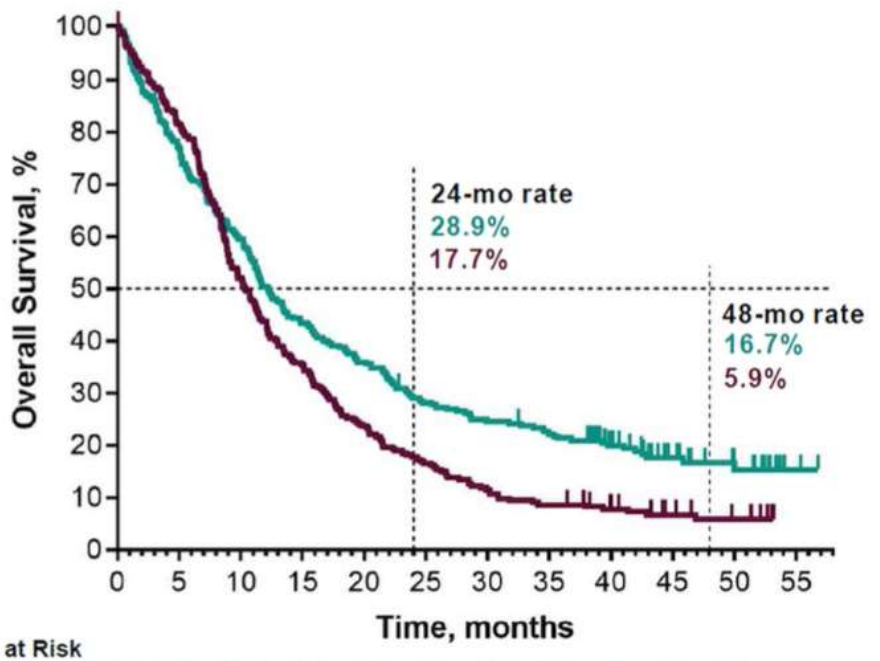


No. at Risk

Pembro	133	107	85	66	58	45	39	36	30	17	9	2
EXTREME	122	100	65	43	29	23	17	13	11	7	4	0

PD-L1 CPS ≥1

	Events	Median OS, mo (95% CI)	HR (95% CI)	*P* value[a]
Pembrolizumab	81.7%	12.3 (10.8-14.8)	0.71 (0.61-0.89)	0.00080
EXTREME	92.9%	10.4 (9.0-11.7)		



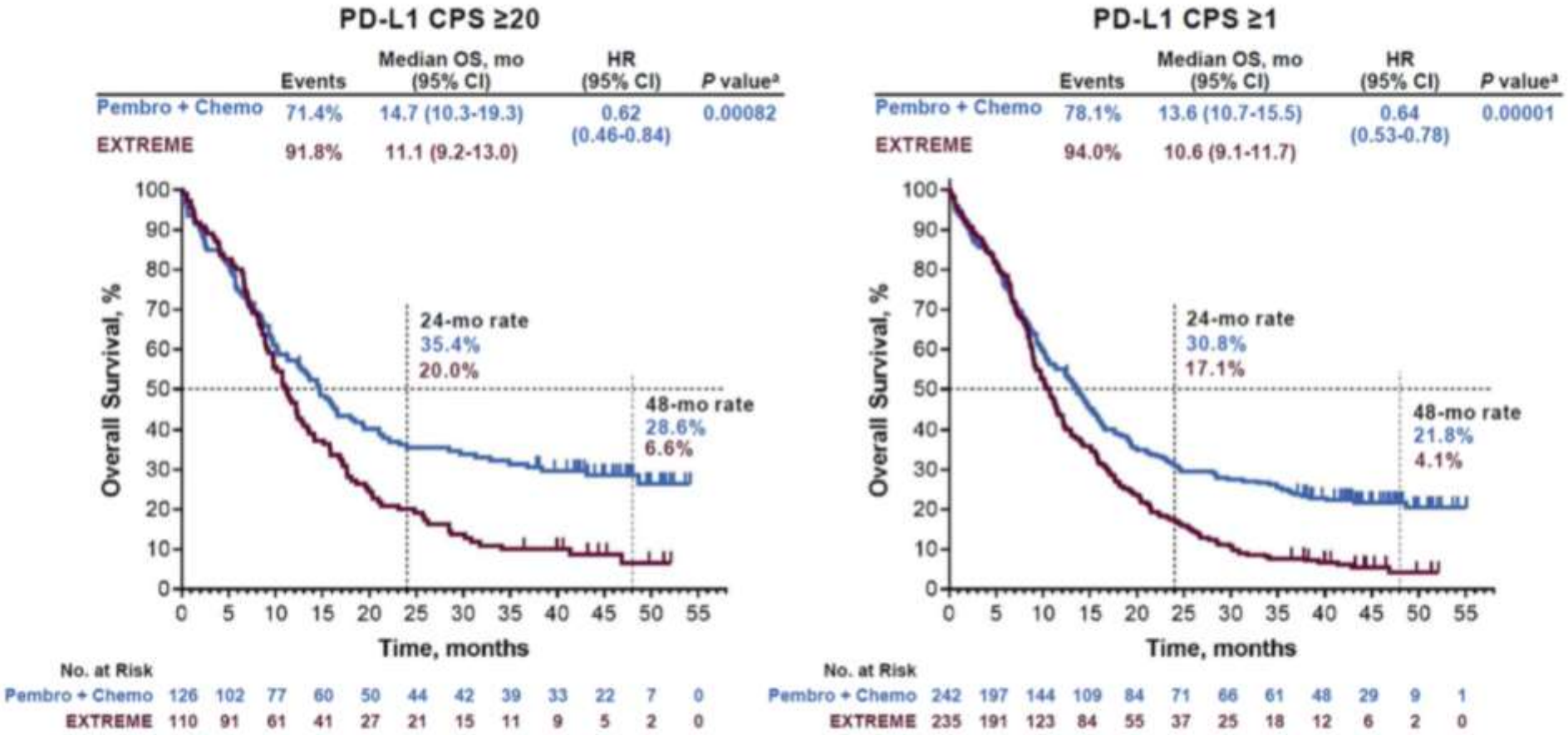
No. at Risk

Pembro	257	197	152	111	92	71	62	55	40	22	12	2
EXTREME	255	207	132	90	60	42	29	22	16	10	6	0

CI, confidence interval; HR, hazard ratio.
[a]Nominal, unadjusted one-sided *P* value based on log-rank test. Data cutoff: February 18, 2020.

Greil R et al. ESMO 2020. Abstract 915M0.

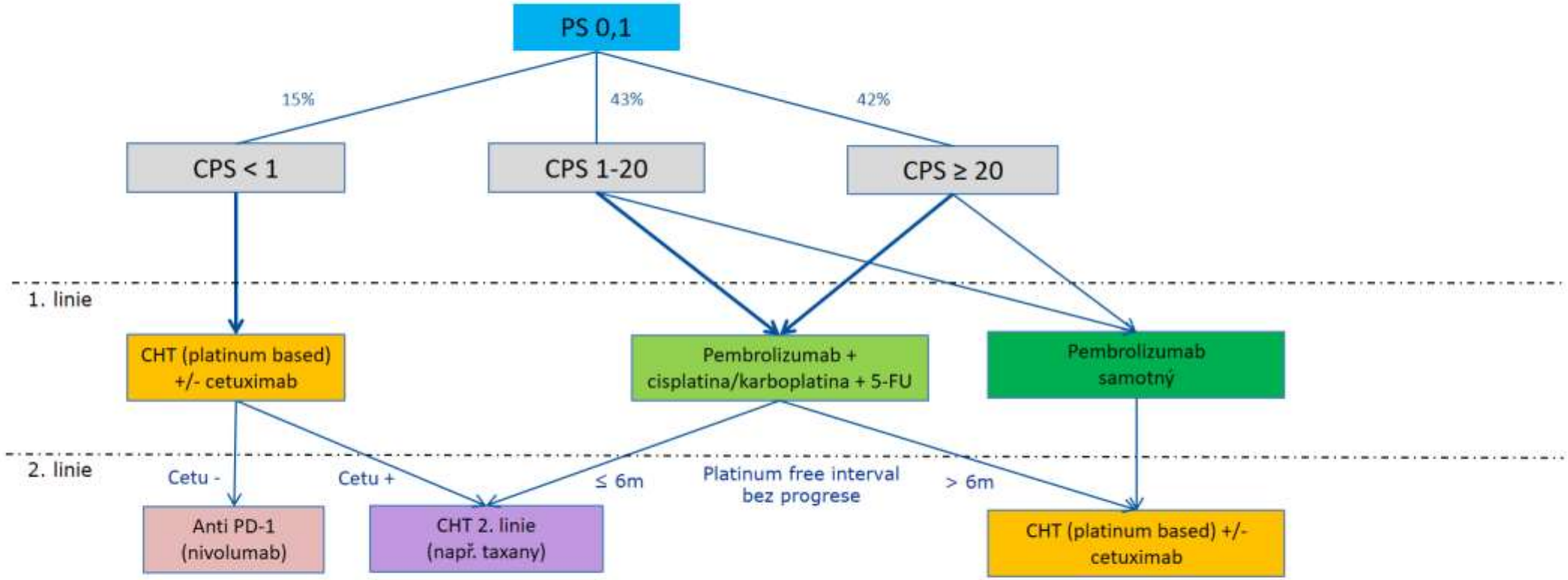
4-Year OS: Pembrolizumab + Chemo vs EXTREME



[a]Nominal, unadjusted one-sided p-value based on log-rank test. Data cutoff: February 18, 2020.

Greil R et al. ESMO 2020. Abstract 915M0.

R/M SCCHN, evidence based, ovšem co nám povolí úhrady SÚKL a ZP



- Cetuximab je hrazen pouze u nádorů dutin ústní
- Nivolumab není hrazen po předchozím podání cetuximabu

Best supportive care

Take home message #2

- Imunoterapie na blokády principu imunitních kontrolních bodů se uplatňuje i rekurentních a metastatických nádorů hlavy a krku
- Prediktorem volby systémové léčby je PD-L1 exprese (CPS)
- Kombinace pembrolizumab + chemoterapie je spojená pravděpodobně s větší šancí na dlouhodobé přežití (nepřímé srovnání)

Karcinom nazofaryngu

Intergroup trial 0099

- konkomitantní a adjuvantní chemoterapie k RT u lokálně /regionálně pokročilých nádorů nasofaryngu versus radioterapie samotná

- statisticky významné prodloužení 3-y PFS (69% vs. 24%, p<0,001) i 3-y OS (76% vs. 46%, p<0,001)

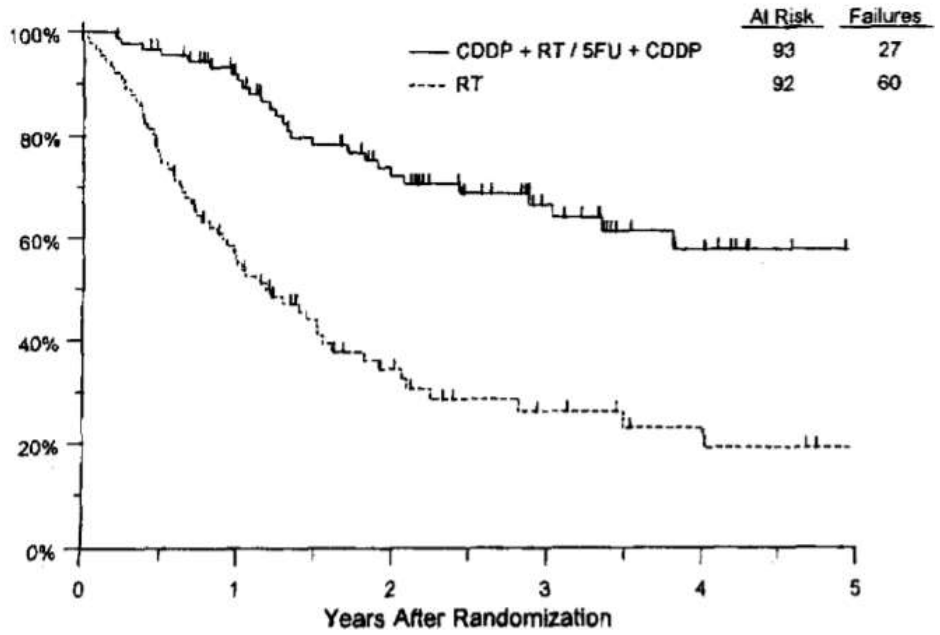


Fig 4. PFS for randomized patients on RT only and combined CT/RT.

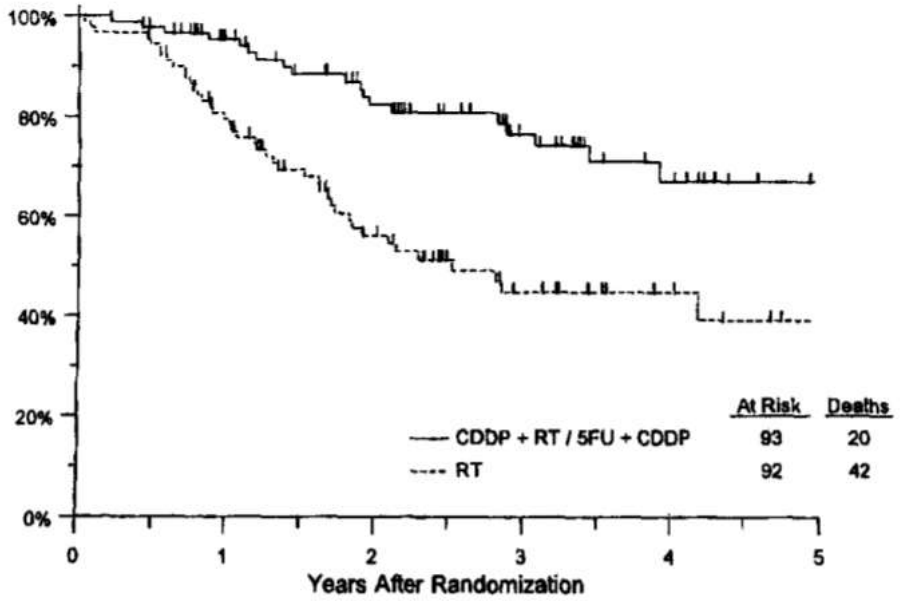
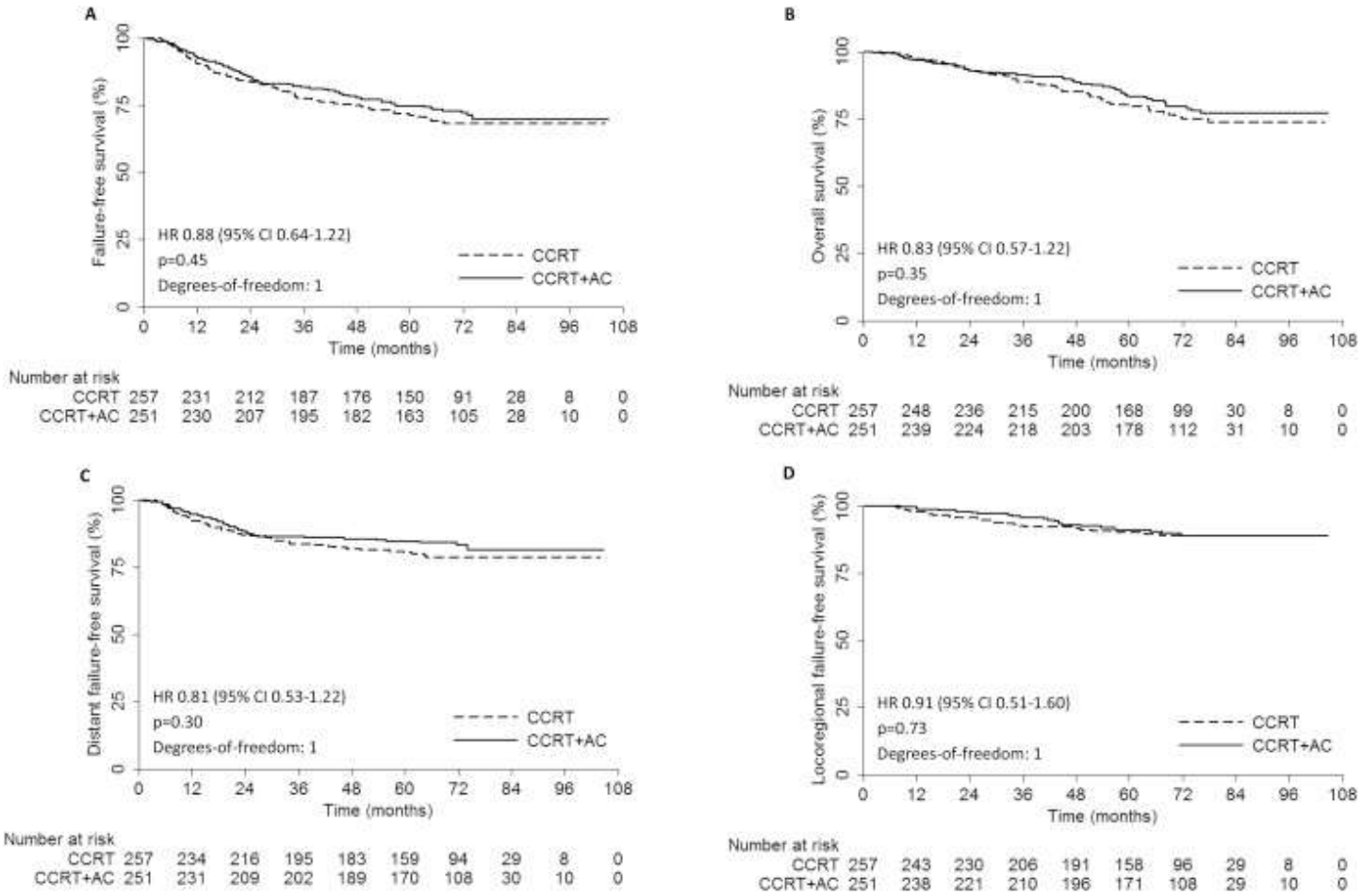


Fig 3. Overall survival for randomized patients on RT only and combined CT/RT.

Al-Sarraf et al. JCO 1998

Nádory nazofaryngu

- Randomizováno **508 pacientů**
- CHRT samostatně vs. CHRT + adjuvantní CHT
- CHRT - cDDP 40 mg/m^2 weekly
- Adjuvantní CHT cDDP 80 mg/m^2 + 5FU 800 mg/m^2/d x5 3 cykly á 4 týdny



Conclusion: Adjuvant cisplatin and fluorouracil chemotherapy still failed to demonstrate significant survival benefit after CCRT in locoregionally advanced NPC based on the long-term follow-up data,

Chen et al. Eur J Cancer 2017

Nádory nazofaryngu

Indukční CHT + CHRT vs. CHRT samostatně

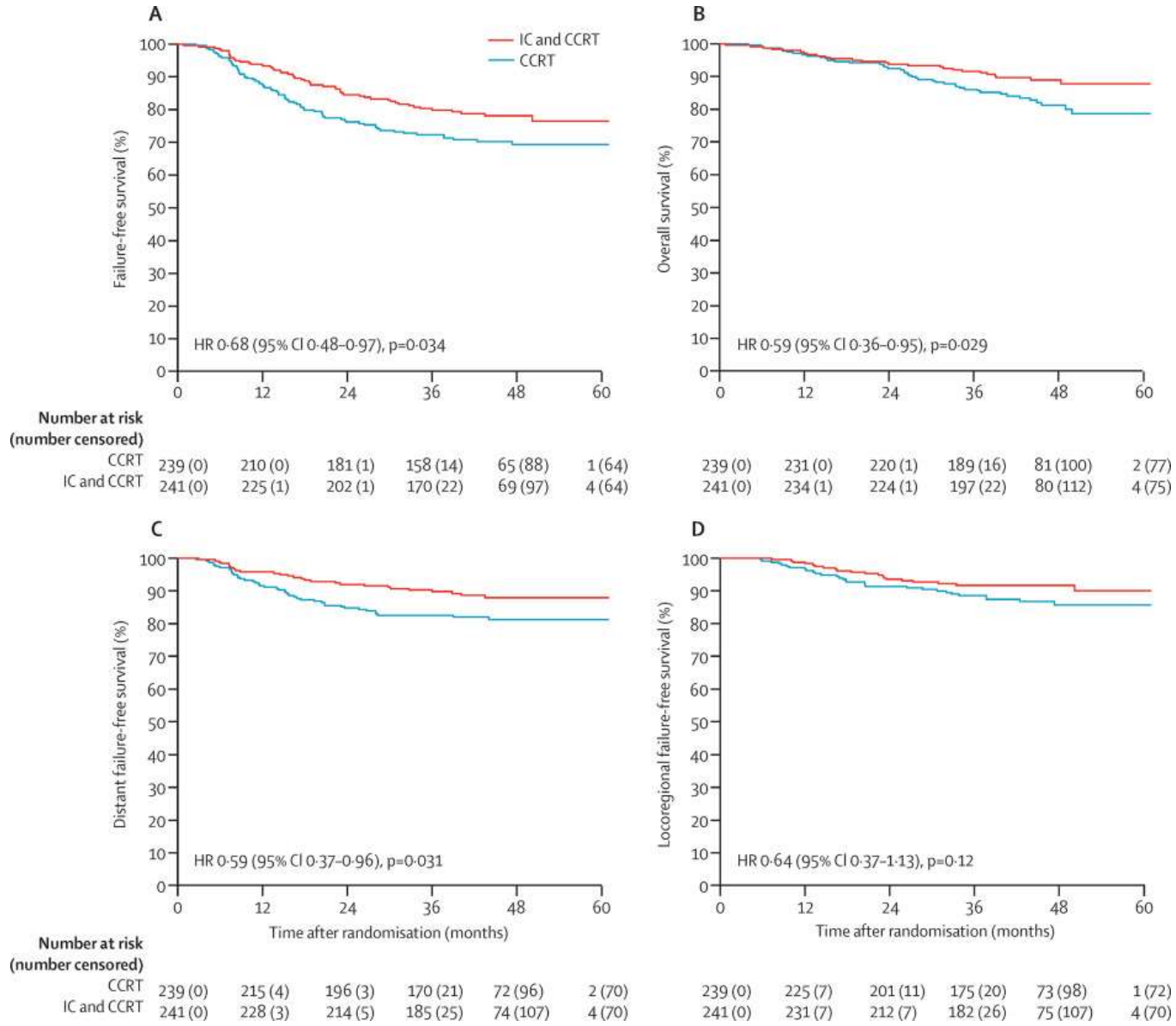
Randomizovaný čínský trial fáze III, 480 pacientů

- **Indukční CHT režim TPF + CHRT**
- vs. **CHRT** (3x cDDP 100mg/m2)

- Indukční CHT TPF zlepšuje proti samotné CHRT:

- failure-free survival
- distant failure-free survival
- overall survival

s přijatelnou toxicitou



Sun et al. Lancet Oncol. 2016

Nádory nazofaryngu

<u>Indukční CHT + CHRT vs. CHRT samostatně</u>

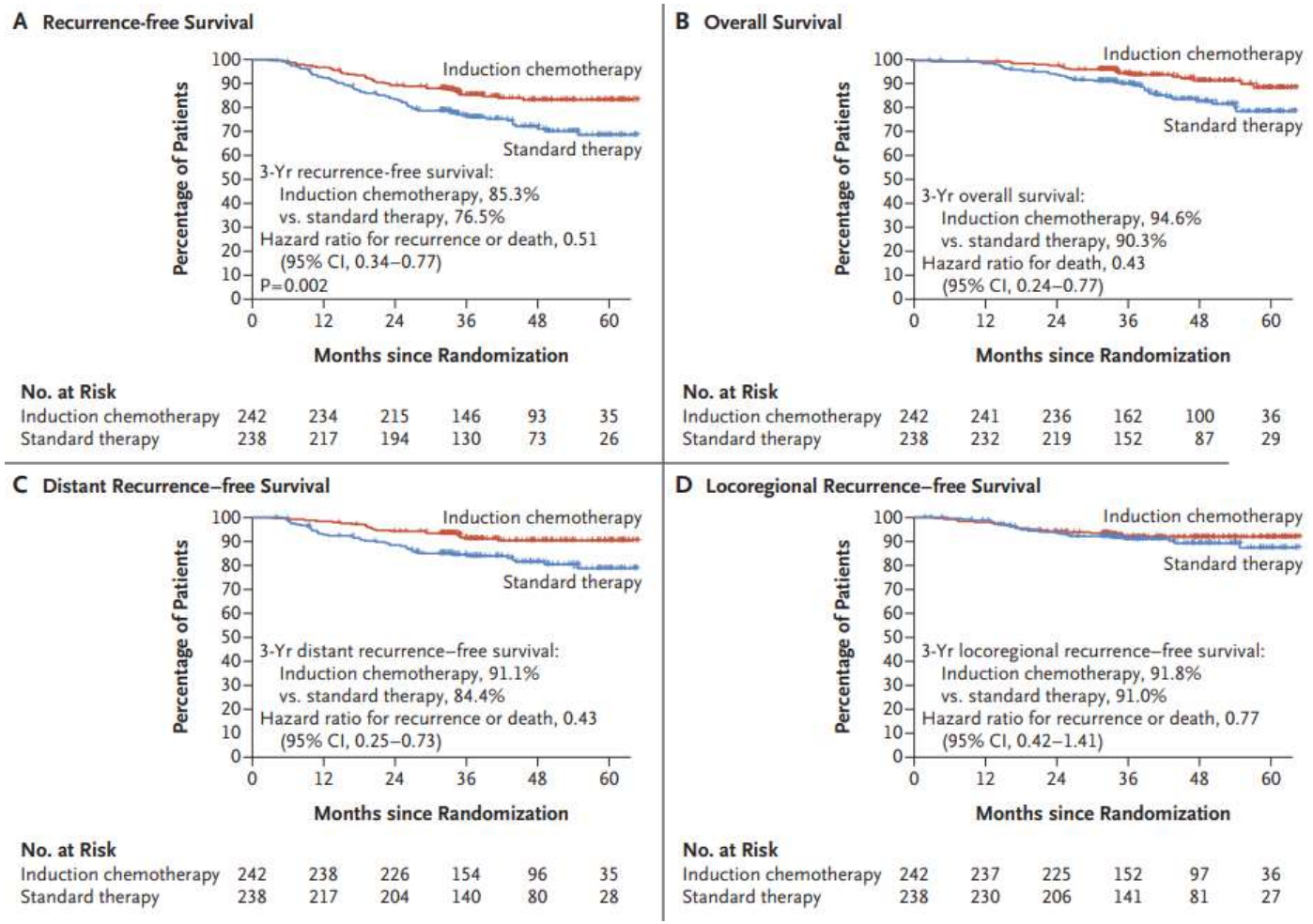
Randomizovaný čínský trial fáze III, 476 pacientů

- **Indukční CHT režim GP + CHRT**
- vs. **CHRT** (3x cDDP 100mg/m2)

- Indukční CHT GP zlepšuje proti samotné CHRT:

- recurrence-free survival
- distant recurrence-free survival
- overall survival

s přijatelnou toxicitou



Study Design

Participants

- Aged 18-65
- Histologically confirmed as WHO II/III NPC
- T1-4N2-3M0 (AJCC 7th)
- ECOG score: 0-1
- Adequate hematological, renal, hepatic function

R 1:1

PF arm

CCRT : RT* + DDP 100 mg/m², D1, Q3W, 3 Cycles

Adjuvant Therapy: DDP 80 mg/m² D1+ fluorouracil 4 g/m² by 96-h infusion, every 4 weeks, 3 Cycles after the end of RT

Stratified by

- Treatment Center
- Nodal (N) Category (N2 or N3)

GP arm

CCRT : RT* + DDP 100 mg/m², D1, Q3W, 3 Cycles

Adjuvant Therapy: DDP 80 mg/m², D1 + gemcitabine (1 g/m²) D1 and D8, every 3 weeks, 3 Cycles after the end of RT

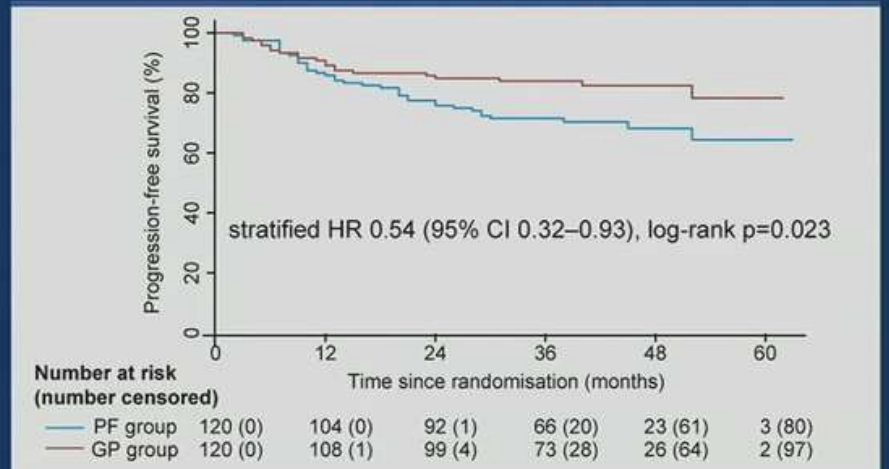
The time interval between CCRT and AC is 4 weeks

*RT: PTVnx: 70Gy/33F, PTVnd: 64-70Gy/33F, PTV1: 60Gy/33F, PTV2: 54Gy/33F

PRESENTED BY: Lin-Quan Tang, MD, PhD

3-year PFS for ITT analysis

GP group reduced risk of progression or death than that in PF group

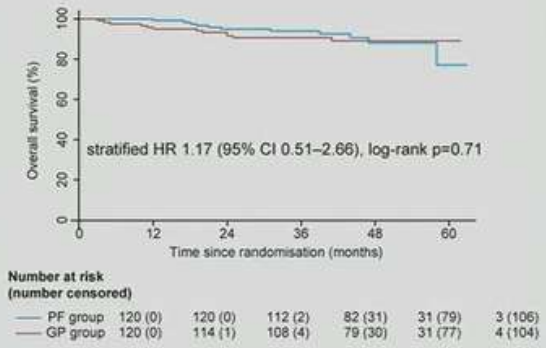


Group	Intention-to-treat population		
	3-year PFS	95% CI	$P_{log\text{-}rank}$
PF group	**71.5%**	62.5-78.7 %	
GP group	**83.9%**	75.9-89.4 %	**0.023**

OS, LRFS, DMFS for ITT analysis

GP group reduced risk of LRFS and DMFS, but has no effect on 3-year OS

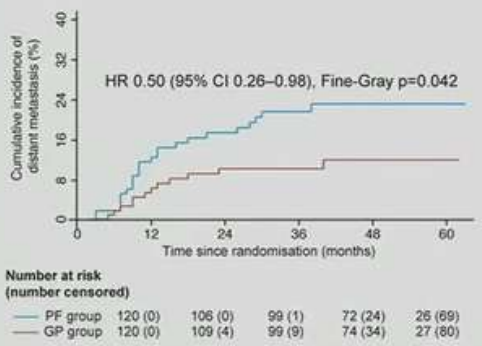
GP group exhibited no effect on 3-year OS than that in PF



Number at risk (number censored)

PF group	120 (0)	120 (0)	112 (2)	82 (31)	31 (79)	3 (106)
GP group	120 (0)	114 (1)	108 (4)	79 (30)	31 (77)	4 (104)

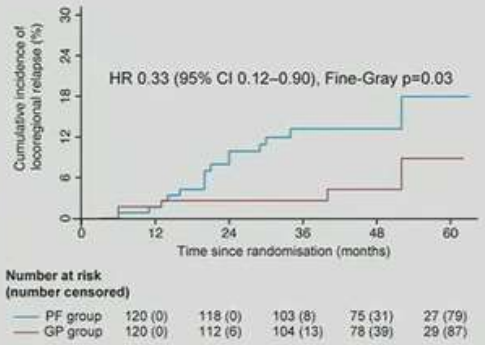
GP group reduced risk of distant metastasis than that in PF



Number at risk (number censored)

PF group	120 (0)	106 (0)	99 (1)	72 (24)	26 (69)	3 (92)
GP group	120 (0)	109 (4)	99 (9)	74 (34)	27 (80)	3 (104)

GP group reduced risk of locoregional relapse than that in PF



Number at risk (number censored)

PF group	120 (0)	118 (0)	103 (8)	75 (31)	27 (79)	3 (102)
GP group	120 (0)	112 (6)	104 (13)	78 (39)	29 (87)	3 (112)

* OS = overall survival; LRFS = locoregional relapse-free survival; DMFS = distant metastasis-free Survival

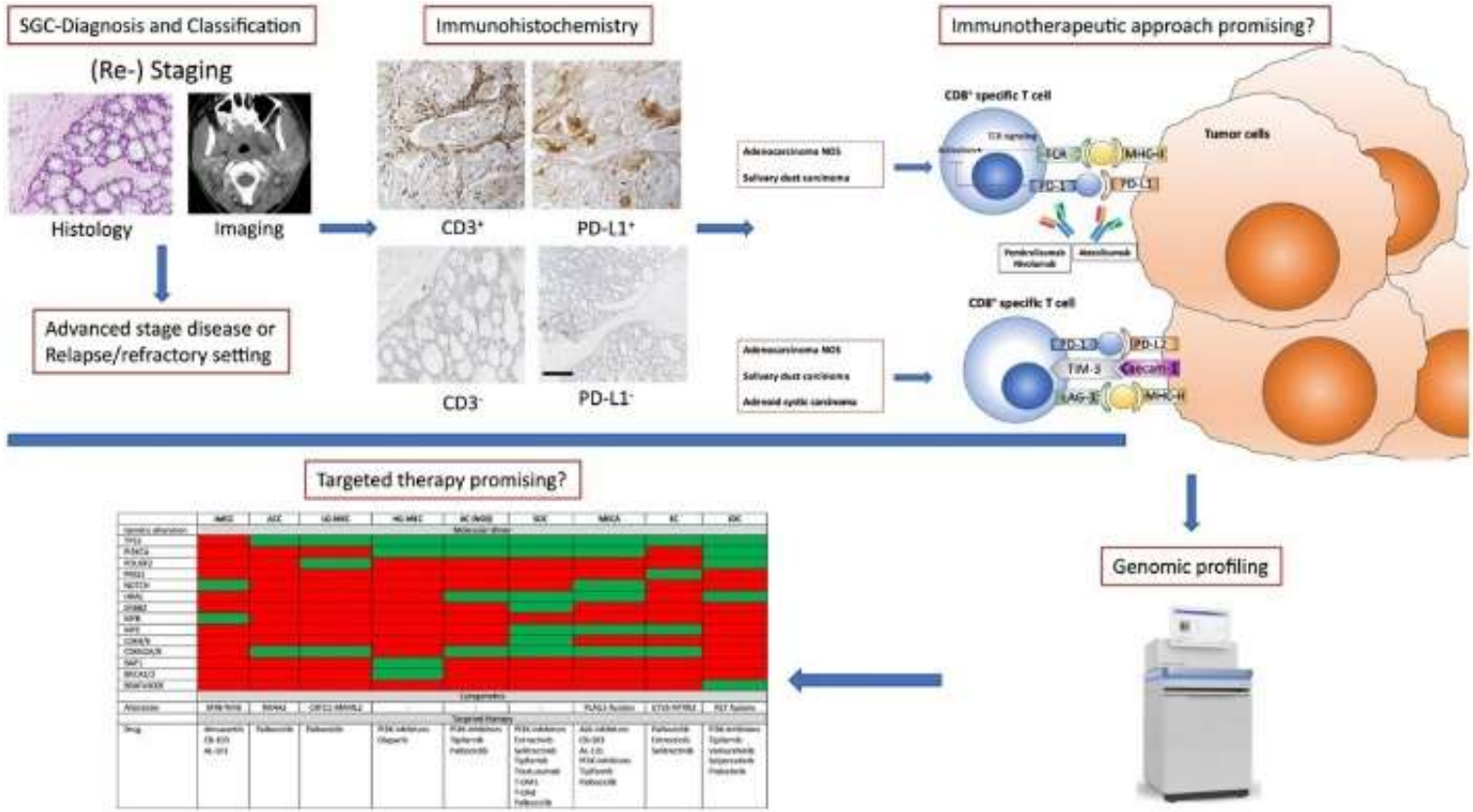
Take home message #3

- Standardem léčby lokálně a regionálně pokročilých skvamózních karcinomů nosohltanu je chemoterapie v kombinaci s neoadjuvantní nebo adjuvantní chemoterapií.

- Za standard neoadjuvantní nebo adjuvantní chemoterapie lze nově pokládat kombinaci gemcitabin-cisplatina

Nádory slinných žláz

- Operace +/- RT
- Rekurentní & metastatické tumory
  - úloha molekulárních tumor-boardů
    - anti HER-2 terapie (salivary duct ca)
    - TRK inhibitory (sekreční ca)
    - antiandrogenní terapie
  - sledování (ACC)



Witte HM, Gebauer N, Steinestel K.Crit Rev Oncol Hematol. 2022

Take home message #4

Take home message #4

Take home message #4